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EDITORIAL

A MAN IS AS OLD AS HIS LEGS*

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That a man's prime is past is often signalled by the recognition that his "pins aren't as good as they used to be." If one surveys the situation, it becomes apparent that the structural components of the legs—the skin, muscle, bones and joints—are capable of functioning many years more than the prescribed three score and ten. It is the conducting systems, the nerves and blood vessels, which fail. Until the past decade physicians only recognized the intrinsic neurological and vascular disease processes—such as a polyneuritis, endarteritis or arteriosclerosis—which were present in the legs, as a common cause of impairment of the lower extremities.

Yet many people seemed to have much more incapacity than could be accounted for by the objective findings in the extremities themselves. Such vague neurological conditions as progressive lateral sclerosis, spinal arthritis, cerebral degeneration, etc., were invoked to explain these conditions. Then as the syndromes associated with cervical discs became common knowledge and cervical myelograms were done routinely, it was recognized that disorders of the cervical spine could be an etiological factor in the production of progressive spasticity and weakness of the lower extremities.

Although frank herniation of a cervical disc, usually midline, may cause cervical cord compression, such a disc protrusion is not necessarily present. Degeneration of the disc with proliferation of the adjacent vertebral bodies may produce a lipping or ridging at the interspace which impinges upon the vertebral canal. This condition, termed cervical arthritis, spondylosis or ridging syndrome, is particularly prone to occur in the lower cervical region, between the 5th and 6th, 6th and 7th or 7th cervical and 1st thoracic vertebrae. In roentgenograms of the cervical spine one may see the narrowed disc space and the bony proliferation which may extend laterally into the vertebral foramina or medially into the vertebral canal. However, the ridging per se does not seem to be sufficient to cause a complete obstruction. In some cases a block is present only on hyperextension of the neck. Examination of cervical myelograms show that with extension of the neck the ligamentum flavum, having lost its elasticity of early life, folds on itself anteriorly, causing a bulging into the canal which compresses the spinal cord against the anterior

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ridging. An added factor, present at times, is the occlusion of the blood vessels entering the intervertebral canals by the lateral osteophytes giving rise to an ischemia of the cord itself.

Clinically the syndrome usually presents as a progressive weakness and spasticity of the lower extremities with little wasting or sensory disturbance. The tendon reflexes at the knees and ankles are hyperactive and the plantar reflexes extensor in type. There may be a history of arm pain suggesting an earlier disc protrusion but often this is absent. In the upper extremities there may be some atrophy of the small hand muscles and occasionally sensory disturbances. The diagnosis may be confirmed by the typical findings in a cervical myelogram of ridging on the anterior surface of the canal and usually the posterior indentations of the bulging ligamentum flavum.

This condition may be helped by a laminectomy, removal of the ligamentum flavum and section of the dentate ligaments which at times hold the spinal cord against the ridges. When the condition has been present for a long period of time irreparable damage may have been done to the long tracts of the spinal cord and the best which may be hoped for may be a prevention of further progression of the diseased state. In less advanced cases some improvement may be expected.

A somewhat analogous condition in the vascular system is, at times, the cause of intermittent claudication. Localized arteriosclerotic aneurysms or occlusions of the lower abdominal aorta may produce vascular insufficiencies of the legs. Clinically intermittent claudication, hip pain and weakness of the legs are presenting complaints. Obliteration of the femoral pulse and slow filling of the vessels of the leg after elevation are the prominent clinical findings. The obstructive nature of the lesion can be diagnosed and accurately localized by aortography. In recent years the vascular surgeon has devised techniques whereby the diseased portion of the aorta may be removed and a homologous graft or synthetic tube may be used for reconstruction of the aorta. Localized arteriosclerotic aneurysms or occlusions of the lower abdominal aorta may be treated successfully by these techniques with little risk and the prospect of giving a longer and happier life span.

These advances in the understanding of the mechanisms impairing the function of the legs have given a new impetus to the surgical prevention of debilitation in the aged. With the increasing number of people who are surviving to old age, it behooves the physician to be on the lookout for such neurological and vascular syndromes which may be benefited, at times spectacularly, by surgical intervention.

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Report

COMMITTEE FOR THE STUDY OF PELVIC CANCER*

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Secretary

The Committee for the Study of Pelvic Cancer meets on the third Thursday of each month from 5-6 P.M., in the Small Hall of the Medical and Chirurgical Faculty Building. Selected cases are presented for discussion. All physicians are invited to attend the meetings.

Abstracts of Case Discussions:

CASE I. M. White. Age: 41 years. Married. Gravida 8. Periods said to have been regular. Vaginal discharge for many years but this markedly increased during the summer of 1954. In November, onset of continuous reddish-brown discharge. Consulted doctor A in early January 1955. Pelvic examination was made and the patient told that "something was wrong with the mouth of the womb." She was advised that operation was the best treatment but that the condition could be treated by "burning." For financial reasons the patient elected to have the treatments. She went to doctor A for treatment twice a week to March 11th, when she was told that the condition was better but might recur and that she should go to the hospital. She was seen in the hospital clinic on March 31st where a biopsy was taken and arrangements made for admission for radium application. Referred to second hospital for x-ray therapy.

Diagnosis: Squamous cell carcinoma, cervix, clinical stage I.

Chairman: On the basis of the information obtained from the patient and given in the abstract, there was patient delay in this case and further delay on the part of the doctor in getting the patient to the hospital.

Doctor A is unable to be present at the meeting today but we have some further information from him received by telephone. He reports that the patient first came to him in January of this year. On examination, "the cervix was a terrible mess." He tried to clean it up in order to get a better look at it and did cauterize the cervix. He told the patient that it would be best for her to go to the hospital for operation but because of family problems and finances she did not want to do this. He said frankly that he did not know whether she had a malignancy or not but regrets that he did not get her to the hospital earlier. Incidentally, he asked for advice as to what can be done with "these stubborn women who don't want to go to a hospital."

Is there any comment on this case?

Committee member: My feeling is that any cervix which is bad enough to cauterize is bad enough to biopsy. Certainly at least a cytological smear should have been taken.

Committee member: Do you feel that taking a biopsy is an office procedure for a man in general practice?

Chairman: I know that some doctors hesitate to do this and I believe this physician mentioned that he did not feel qualified to do this in his office. However, I feel that it is a relatively easy procedure and that a general practitioner should be qualified to do it. There are two laboratories in the city easily available for the pathology, if the patient cannot afford a pathological fee.

Visiting physician: Certainly it would seem if a doctor can cauterize a cervix, he can take a biopsy.

Visiting surgeon: You still have not answered this physician's question as to what to do with "stubborn women."

Chairman: I can only tell him what I do with them. If a patient is hesitant in following advice or prescribed treatment, I feel you have to be increasingly blunt in telling her the diagnosis or suspected diagnosis. If necessary, state the diagnosis frankly. Or, refuse to treat the case if the patient is not willing to follow the prescribed treatment.

Committee member: We have had a few patients in the clinic who refuse treatment even after they have been told the diagnosis.

* Under the auspices of the Medical and Chirurgical Faculty and the Maryland Division of the American Cancer Society.

Chairman: I know that will happen occasionally but you still have to make every effort to get the diagnosis established as soon as possible. In the case under discussion the diagnosis was not made.

CASE II. D. W. White. Age: 56 years. Married. Gravida 4 0 2 2. Menopause in 1949. January 1954, onset of slight vaginal bleeding, gradually increasing in amount. The patient consulted doctor A in April 1954 and was hospitalized for a D. & C. The diagnosis was adenocarcinoma, fundus uteri, grade III. A total abdominal hysterectomy was performed. January 1955, recurrence of the carcinoma in the vaginal vault. The patient was referred to doctor B and treated with radium and deep x-ray therapy.

Chairman: This case brings up the question of pre-operative radium in the treatment of carcinoma of the fundus. I know there is considerable difference of opinion concerning this. Since we have made the use of pre-operative radium a routine procedure at the Johns Hopkins the incidence of recurrence in the vaginal vault has been very markedly reduced. I personally have not had one recurrence. In this same period I have seen recurrences in patients not irradiated—that is in patients who were first treated elsewhere and then referred to me or to the clinic regarding recurrences. What has been your experience?

Committee member: Off hand I can think of about four cases which were treated with pre-operative radium and later had vaginal recurrence. Certainly the incidence of recurrence has been greatly reduced with the routine pre-operative use of radium. I do not believe there is any question about that.

Chairman: I know of at least one prominent gynecologist who believes that if you take a large vaginal cuff in doing a hysterectomy, you do not get vaginal recurrence. He uses this means rather than pre-operative radium to prevent recurrence.

(There was further discussion of the use of pre-operative radium in the treatment of carcinoma of the fundus. It was felt that this was particularly useful in the case of a large uterus and made subsequent operative procedure easier.)

Visiting surgeon: In cases where carcinoma is not suspected at the time of the diagnostic D. & C. and radium is not available in the hospital, what would you do?

Chairman: The best of men are fooled. Unless you get a tremendous amount of markedly friable stuff on curettage, the diagnosis is not certain. Why not wait for the report of the pathologist?

Visiting surgeon: If you do a hysterectomy and find carcinoma in the removed specimen, do you follow with deep x-ray therapy?

Chairman: If it is a very early lesion, I would not use x-ray. If it is a large lesion, I would follow with x-ray. Any large lesion, however, should be diagnosed before hysterectomy is performed.

Visiting surgeon: In the particular case under discussion, the lesion was diagnosed and the patient was being treated in a hospital where radium was available.

Chairman: I feel this patient should have had pre-operative radium. However, there are excellent gynecologists who do not go along with this opinion. I believe there could be criticism if we classify such a case as "inadequate treatment."

Visiting surgeon: I believe the consensus over the country is that a patient with adenocarcinoma of the fundus should get intracavitary radium. If this is true, I think the case should be classified "inadequate treatment."

Chairman: At least we can say that it is the consensus of the Committee and those present at this meeting, that pre-operative radium is the best procedure in the treatment of adenocarcinoma of the fundus.

CASE III. A. S. White. Age: 64 years. Widow. Gravida 3. Menopause, 1943. Late September 1954, onset of vaginal bleeding and lower abdominal pain. The bleeding was continuous and profuse at times. Consulted doctor A in early October and was hospitalized for a D. & C. on October 14th. The diagnosis was carcinoma of the body of the uterus. The patient had radium application on October 19th. Pan-hysterectomy and salpingo-oophorectomy on October 25th.

Chairman: There was no delay in this case. It is listed as of interest because the surgery was performed one week after the application of radium. Is there any discussion regarding this case?

Radiologist: I would certainly feel that the radium had not done its work.

Chairman: What is your opinion as to the length of time the radiation reaction continues?

Radiologist: A minimum of three weeks.

Committee member: There is considerable argument as to how long the radiation reaction con-

tinues, but I do not know of anyone who says that the radium is effective within one week.

Visiting surgeon: There is literature advising operation within forty-eight to seventy-two hours after radium. I have actually seen only one case so treated. The uterus grossly looked as if no radium had been used at all.

Chairman: The surgeon concerned in this case expected to be here today but apparently was unable to come. We do have some additional information from him received by telephone. This patient had a mass which was large and fungating and the bleeding was quite profuse. The patient was irradiated by an oncologist. The bleeding abated somewhat but within a few days was again rather profuse. In consultation, the oncologist advised that they go ahead with surgery. He felt that the radium had done its work. The surgeon says he believes the usual procedure is to wait a month or six weeks following radiation and he would have done this except for the continued bleeding and the advice of the oncologist. He would like to know the opinion of the Committee regarding this.

The opinion of the Committee was very definitely that the radium had not done its work within one week. It was felt that the emphasis of all evidence at hand indicates a long period of radiation reaction. Although there are differing opinions throughout the country as to the length of time during which radiation reaction occurs, it was the unanimous opinion of the Committee that surgery should not be performed until a month to six weeks following radiation.

CASE IV. E. C. Colored. Age: 61 years. Married. Gravida 4. Menopause, 1954. October 1954, patient seen in gyn. clinic with complaint of burning pain in epigastrium with occasional radiation. Cervix said to be negative and the impression was, "No gyn. pathology." May 1955, patient seen in medical clinic regarding abdominal pain and referred for gynecological consultation because of history of intermittent vaginal discharge for one month and one episode of spotting during this time. Examination revealed slight erosion on the cervix, and bleeding on instrumentation. Biopsy showed intraepithelial carcinoma. Repeat biopsy confirmed this diagnosis. The patient was admitted to the hospital and scheduled for a modified Wertheim. At operation the diagnosis was carcinoma of the cervix, stage II, and a radical Wertheim was done. Deep x-ray therapy postoperatively.

Chairman: This is an unfortunate case but the kind of thing that will occur occasionally, particularly if the disease extends up into the cervical canal. When we were doing Wertheims routinely we often found the disease more extensive than was anticipated. This was one of our reasons for changing the therapy to radium and x-ray rather than surgery.

Committee member: As you know, this is one of our cases. The two biopsies seemed to indicate definitely intraepithelial carcinoma, and the decision was to go ahead with surgery without carrying out any other diagnostic procedures. In these intraepithelial cases a conization is usually done before surgery but it was not done in this case. When the patient was examined under anaesthesia there did not seem to be any reason to change the diagnosis and no further extension of the disease was made out.

Visiting surgeon: Was there anything visible on the cervix?

Committee member: I have here the report on the examination in the clinic on June 6th. "On visualization of the cervix, it is seen to be small and conical. There are no obvious lacerations. Immediately around the os for a distance of several m.m. all the way around is a granular erosion which bleeds on contact. Uterus two to three times enlarged and slightly irregular. The adnexae are entirely negative. The entire pelvic anatomy is perfectly mobile. No fixation and no suggestion of any induration in the parametria."

At operation, considerable difficulty was encountered on the left side in getting the operative specimen out. The operative note reads, ". . . on the left side the parametrium for the first time was noted to be thickened and it was thought that there was a myoma of the cervix on the left side—this was represented by a very firm area measuring three cm. in diameter and seemed to be protruding from the left aspect of the lower segment of the cervix. On the left side great difficulty was encountered and the left ureter was bared and had to be retracted laterally in order to clamp on the cardinal ligament on this side. . . . Because of the great difficulty on the left and the abnormal appearance of the left parametrium, the uterus was opened and on opening the uterus it was obvious that this patient had a lesion which was more advanced than an intraepithelial carcinoma. The endometrial cavity was covered with an obviously granular lesion which

covered the entire posterior wall and extended through the cervical canal to appear as a tiny erosion on the exterior cervical os."

At this point the resident called me in consultation. It was decided to do a pelvic lymphadenectomy.

Chairman: In looking back on the case, the thing that really fooled you was the mass in the broad ligament which was taken for a fibroid.

Visiting surgeon: Would the fact that this patient was 61 years old make you wonder as to the diagnosis of intraepithelial carcinoma?

Chairman: No, I do not think so at all.

Visiting surgeon: In New York the staging is not done until the patient is examined under anesthesia. What did the examination under anaesthesia reveal in this case?

Committee member: The operative note gives this report: "Vagina and glands negative. Cervix, large, firm and freely movable. The uterus was normal in size, in mid-position. The adnexal areas negative and no lateral induration noted."

Committee member: I missed this one in recommending surgery without a cold conization. A conization would have established the diagnosis.

Chairman: There are some gynecologists who advocate routine conization. Paul Young and Allen Barnes do this. Paul Young does it for therapy. In Cleveland, they never biopsy but rely on smears and then conization.

Once the diagnosis is established I feel the advantage of the Modified Wertheim for intraepithelial carcinoma is that you get a big vaginal cuff. I have recently had a case in which every place biopsied on the cervix showed intraepithelial carcinoma. At operation I decided to take a little more vaginal cuff than usual and this vaginal cuff also showed intraepithelial carcinoma. I think I got it all. If the patient does get any recurrence, it will be the first one I have had.

Getting back to the case under discussion, how do you think it should be classified?

Committee member: It is not "delay" and I do not believe that you can say it is "inadequate treatment." The patient had a radical Wertheim and deep x-ray therapy post-operatively. There was nothing more that could have been done.

Committee member: It is not exactly the treatment we advocate for a stage II, carcinoma of the cervix. You may recall that we had a case somewhat similar to this sometime ago. In that case the possible extension of the disease was found before the operative specimen was out, and I advised the resident to "back out" and leave the uterus and cervix to be treated by radiation. In this case today, the specimen was out before the extension was known.

Chairman: I guess we shall have to extend our classification to include "improper treatment" as well as "inadequate treatment."

I would like to mention in connection with this discussion of Wertheim procedures, that there are some interesting figures in the "Annual Report on the Results of Treatment in Carcinoma of the Uterus" recently published by Dr. Heyman. This report covers statements of results obtained in 1948 and previous years, with the relative recovery rate at the end of five years. It is an extensive report but the statistics which I am referring to concern Boston and Baltimore. In Boston, the study covered cases treated at the Massachusetts General and Pondville Hospitals. In these hospitals the procedure for treatment of Stage I carcinoma of the cervix was a radical Wertheim in selected cases—i.e., thin women under fifty and good surgical risks. Other cases were treated with radium and deep x-ray therapy. Their survival rate at the end of five years was 58.3%. In Baltimore, the study included only cases treated at the Johns Hopkins Hospital. Here the routine procedure was radium and deep x-ray therapy in all cases of stage I—no cases selected—and the apparent recovery rate at the end of five years was 85.7%.

(There was further discussion of surgery versus radiation in the treatment of stage I carcinoma of the cervix.)

Scientific Papers

CARCINOMA OF THE BLADDER*

HUGH J. JEWETT, M.D.†

One of the most perplexing problems in urology is the selection of the best treatment for a given case of carcinoma of the urinary bladder. This is because these tumors vary so widely in lethal capacity that classification according to potential curability has remained elusive. The results of different methods of treatment obviously are not comparable unless the tumors themselves are known to have been comparable. Naturally the best results follow early diagnosis and prompt, adequate treatment, but in this early stage many tumors escape detection because of absent, few, or minimal symptoms. An awareness of what these symptoms are and what they may signify should lead to an improvement in the 5-year survival rate.

Incidence

Carcinoma of the bladder is the most prevalent and important of the malignant tumors of the urinary organs, since cancer of the prostate gland is classified under genital organs. The mortality from vesical cancer begins to rise sharply at about 40 years of age, reaching a peak at 75, and then gradually falls. The disease occurs twice as often in males as in females. No undisputed case of primary malignant epithelial tumor of the bladder has been observed in the very young, but a few have been reported in individuals under the age of 15 years. The death rate per year from vesical cancer is about 3 per cent of the total number of deaths resulting from all types of malignant disease.

Etiology

A compound known as beta-naphthylamine, which is used in certain types of chemical industry, has been proved to be carcinogenic for the bladder, when inhaled, ingested, or rubbed on the skin. Workers inadvertently exposed to, and dogs purposely fed this substance have been found to have cancer of the bladder after a lapse of time. Other chemicals such as benzidine, alpha-naphthylamine, and certain nitro- and amino- compounds have been under suspicion but their carcinogenicity has not yet been proved. Tumors do not develop in dogs to which these substances have been fed, and when tumors occurred in men who had been exposed to them, cross contamination with beta-naphthylamine could not be excluded with certainty.

So far as the general population is concerned the cause or causes of this disease are obscure. The specific, and established, carcinogenicity of beta-naphthylamine has stirred speculation regarding the influence of possible carcinogens which might enter the body by ingestion, inhalation or cutaneous application, from foodstuffs, medicines, cosmetics and clothing, and fumes of various sorts. To date, however, this hypothesis has been reached solely through inference which has resulted from at least two observations. The first is that urinary stasis often is associated with tumors of the bladder and also with tumors of vesical diverticula which cannot empty. The second is that non-invasive tumors of the bladder in a few instances have

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† One of a series of papers from the Maryland Division of the American Cancer Society that will appear from time to time.

been known to regress or disappear after permanent diversion of the urinary stream above the bladder. These observations suggest that the urines in these particular instances may have contained a specific carcinogen which caused malignant proliferation after prolonged contact with the lining membrane. But the identifica-

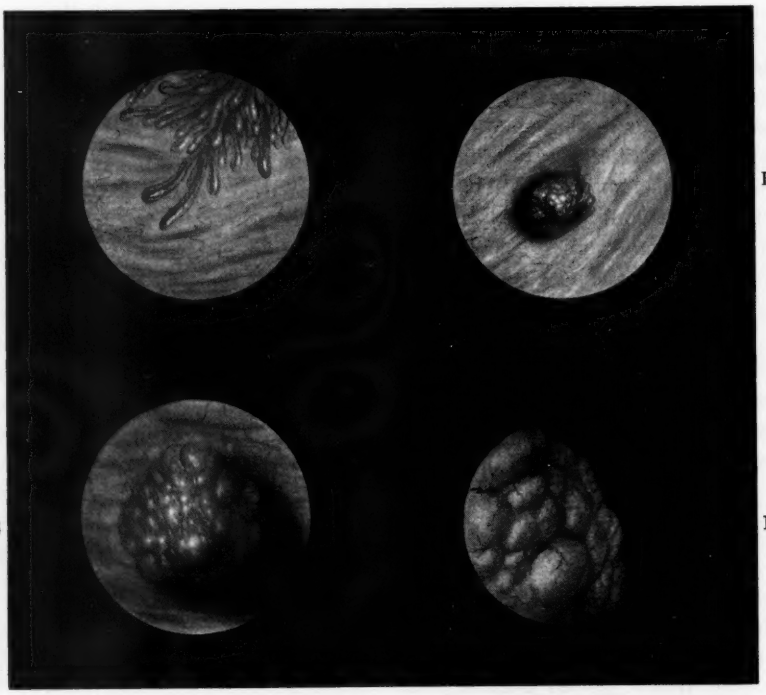

FIG. 1

FIG. 2

FIG. 3

FIG. 4

FIGS. 1, 2 AND 3. Didusch, William P., A Collection of Urogenital Drawings; New York, American Cystoscope Makers, Inc., 1952.

FIG. 4. Young, H. H., and Davis, D. M., Young's Practice of Urology; Philadelphia, W. B. Saunders Company, 1926.

tion of any such compound in the urine has not yet been made, and, at present, irritation and inflammation, with or without stasis, appear to be the most conspicuous of predisposing causes.

PATHOLOGY

Cancer of the bladder generally begins as a microscopic focus of abnormal cellular proliferation upon or within the mucous membrane. It may remain *in situ* (non-invasive) for a variable period and then sprout from the surface of the lining membrane in the form of a tiny villous outgrowth. Connective tissue and blood vessels derived from the submucosa extend into it forming a central core which is covered by epithelial cells. In the case of benign tumors these cells closely resemble those of the bladder mucosa, and the central strand of stroma becomes elongated and filamentous and may branch into numerous feathery processes of considerable length (Figs. 1 and 9). Since malignant degeneration often occurs in these benign tumors, all should be considered potentially malignant.

Malignant tumors are conveniently classified as non-infiltrating and infiltrating. When non-infiltrating they are somewhat similar to the benign tumors, inasmuch as their primary stalk

or pedicle is slender and delicate. The secondary axes or branches, however, are fused to a greater or lesser extent into a fairly compact and globular mass which may appear to rest directly upon the bladder mucosa (Fig. 2). The epithelial cells of the mass, which is attached by a short and often obscured pedicle, show varying degrees of anaplasia.

In the case of infiltrating tumors, malignant cells are present in the pedicle or in the bladder wall, or in both. In about half the cases the invading cells originate in a clearly recognizable pedunculated tumor, although at this stage the pedicle is thickened and unyielding (Fig. 3). In the rest, the non-pedunculated group, no stalk exists. In some of these, however, a stalk may have been present in the beginning, and sloughed after a time from interference with its blood supply. In an early stage the non-pedunculated, sessile tumor may appear as a reddened, granular patch on the mucosa. Later, its flattened, nodular surface may have the appearance of tiny cobblestones (Figs. 4 and 7), and finally it becomes a hard crater-like ulceration with rolled, nodular margins. The principal features of these 4 types of tumors are roughly depicted in Figure 5.

The histologic structure of infiltrating can-

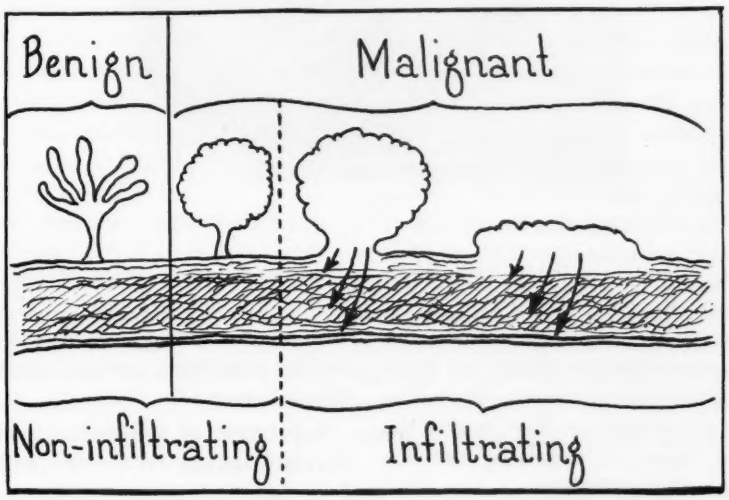

FIG. 5. Jewett, H. J., in chapter on Neoplasms of Bladder. The Cyclopedia of Medicine, Surgery, Specialties; Philadelphia, F. A. Davis Company, 1950.

Infiltrating Carcinoma of Bladder
Relation of Curability to Depth of Infiltration in 107 Autopsy Cases

Group A	Group B	Group C
Submucosal infiltration	Muscular infiltration	Perivesical infiltration
No. of cases 3	No. of cases 15	No. of cases 89
Metastases 0	Metastases 1	Metastases 52
Perivesical lymph only 0	Perivesical lymph only 1	Perivesical lymph only 6
Perivesical fixation only 0	Perivesical fixation only 0	Perivesical fixation only 8
Potentially curable 100%	Potentially curable 86.6%	Potentially curable 26%

FIG. 6

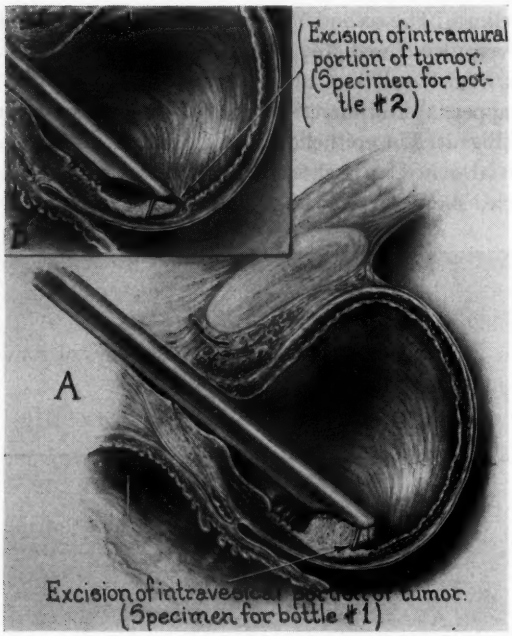
Excision of intramural portion of tumor (Specimen for bottle #2)
A
Excision of intravesical portion of tumor (Specimen for bottle #1)

FIG. 7

cers cannot be reliably predicted from their gross morphology. Roughly, 40 per cent are of the transitional cell type; that is they are composed of cells resembling in greater or lesser degree those of the vesical mucosa, depending on their grade of malignancy. The greater the malignancy, or degree of anaplasia, the less they resemble bladder epithelium.

About 40 per cent are of the epidermoid, or squamous cell, variety. These cells grow in sheets, in which they are in contact with each other. When well-differentiated the cells are polygonal, have sharp margins, and form keratin. When poorly differentiated these characteristics tend to disappear.

Nearly 20 per cent are classified as undifferentiated, since cellular immaturity and anaplasia are marked, and a definite pattern is not discernible. The cells, together with their nuclei, vary greatly in size, shape, and staining quality, and usually are not in contact with one another.

Adenocarcinoma of the bladder is rare, comprising only about 2 per cent of the cases. One form secretes mucus, and though arising in the bladder resembles tumors originating in the digestive tract.

Regardless of histologic classification, infiltrating tumors invade the wall of the bladder, and metastasize sooner or later. The principal sites of metastases in the order of decreasing frequency are the regional retroperitoneal nodes, the liver, the lungs, and the lumbar spine and pelvis. Although metastases do occur in other areas, it is rare to find them elsewhere without concomitant involvement of lymph nodes, liver, lungs, or bones.

From the clinical standpoint it is of vital importance to know whether metastases are present, for curability depends on their absence. Since they are rarely demonstrable prior to operation or autopsy, much effort has been spent in attempting to predict their presence or ab-

sence from the microscopic anatomic structure of the primary growth (Table 1).

Perhaps the best known and most widely used classification for the purpose of shedding light on the prognosis is that of Broders. In 1922, he divided tumors of the bladder into 4 grades of malignancy depending on the extent to which the tumor cells had deviated from normal epithelium. Those that had deviated least were the least malignant and were graded 1. Those that had deviated most were the most immature and anaplastic and were graded 4. Prognosis at times could be predicted with greater accuracy by this system of grading than by the older classifications, but after 14 years of experience the Carcinoma Registry of the American Urological Association found the method in general to be far from dependable. One reason for this lack of dependability is that uniformity in the degree of cellular differentiation throughout the entire tumor exists in only about 50 per cent of the cases in which even multiple, large sections are available for microscopic study. Another reason, perhaps more important, is that the significance of the magnitude of bladder wall invasion has only recently been fully appreciated.

A study of 107 autopsy cases, in which sections had been taken through the bladder wall at the site of deepest penetration by the tumor, showed that the incidence of metastasis and local extension was highest when the penetration was deepest, regardless of gross morphology, microscopic pattern, or degree of cellular differentiation (Fig. 6). The histopathology of the tumor reveals only its potentiality for rapid growth and metastasis, but the presence or absence of spread beyond the bladder is primarily related to the depth to which the tumor has penetrated the bladder wall (Tables 2 and 3). From the clinical standpoint of prognosis, therefore, the first and major division in the classification of these tumors must be between the superficially and the deeply infiltrating varieties. The extent to which the tumor has invaded the bladder wall is governed not only by its degree of cellular activity (its "speed"), but also by its duration in the bladder; that is, its age.

TABLE 1

	Primary Tumor	Metastases	
Papillary carcinoma	40	12	
Poorly differentiated	18	6	33%
Epidermoid carcinoma	39	22	
Poorly differentiated	24	16	67%
Undifferentiated carcinoma	18	15	83%
Total	97	49	

Jewett, H. J., in chapter on Tumors of Bladder, Meredith Campbell's Urology; Philadelphia, W. B. Saunders Company, 1955.

TABLE 2

Histologic Classification of Eighty-one Tumors in Group C

	Primary Tumor	Metastases
Papillary carcinoma	28	11
Epidermoid carcinoma	35	22
Undifferentiated carcinoma	18	15

TABLE 3

Histologic Classification of Fourtern Tumors in Group B

	Primary Tumor	Metastases
Papillary carcinoma	10	1
Epidermoid carcinoma	4	0
Undifferentiated carcinoma	0	0

SYMPTOMS

Hematuria is reported to be the presenting symptom in 68 to 80 per cent of the cases. It may be slight or profuse, transient or persistent, early or late in the course of the disease. Usually it is painless, but at times very painful when clots are passed. Characteristically the urine is uniformly bloody, but occasionally the blood may appear only at the beginning or at the end of urination. The degree of hematuria bears little relationship to the gravity of the situation, and therefore slight hematuria may prove deceptive to both patient and physician. In a study of 860 cases of hematuria reported by Kretschmer (1925), 38 per cent were found to arise

from tumors of the urogenital tract, and 28 per cent of the 860 cases from tumors of the bladder.

Frequency of urination occurs in nearly one-third of the cases of infiltrating cancer, and may or may not be associated with ulceration or infection. In advanced cases there may be obstruction at the bladder neck, pain in the bladder, rectum, pelvis, flank, back or leg, edema of the leg from venous obstruction, and occasionally symptoms of urosepsis and uremia from ureteral obstruction.

Diagnosis

Hematuria and vesical irritability are the most frequent and important symptoms of bladder cancer, but blood may be present even when unnoticed by the patient. In 73 cases in which no other urogenital disease could be found after complete urologic investigation, gross hematuria was present in 65, and occult hematuria in 6. In only two were erythrocytes absent from the centrifuged urinary sediment.

Although hematuria and frequency result more often from conditions other than bladder cancer, especially in women, the possibility of malignancy of the bladder should be considered in an adult over 40, if the urine contains no tubercle bacilli, the prostate gland and its secretion are normal, and the plain roentgenogram and urogram show nothing remarkable. When there is no other obvious cause, a thorough urologic investigation will be rewarding in a sufficient number of cases to justify it. The treatment of hematuria and frequency of urination without first demonstrating their cause is to be condemned. The prompt disappearance of hematuria after oral or parenteral therapy does not necessarily exclude the presence of tumor, since bleeding is often characteristically transient and intermittent. The real danger lies in the creation of a false sense of security which results in the postponement of definitive diagnosis, and often allows the tumor to reach an advanced and incurable stage before it again calls attention to itself.

At the present time the study of stained smears of the urinary sediment for exfoliated cancer cells is of little practical value to the busy practitioner. Not only is previous training in special cytological techniques and diagnosis required, but also prolonged and painstaking study of each specimen for characteristic cells. This in itself may involve numerous preparations and hours of laborious search. It is simpler and more satisfactory to examine the bladder with the cystoscope.

Physical Examination. Hematuria, gross or microscopic, with or without frequency of urination, for which there is no obvious cause, should lead to further investigation, unless it is contraindicated for some special reason. The renal and bladder areas are palpated for mass or tenderness, and the prostate gland, seminal vesicles, and bladder base are examined digitally. If possible the prostatic secretion is obtained for microscopic study, but examination of the urine for tubercle bacilli may be postponed, pending further findings.

Roentgenography. If the symptoms and signs are still unexplained, a plain roentgenogram (KUB) and an excretory urogram (IVP) then may be indicated. These films help exclude urinary or prostatic calculus, renal tumor, ulcerative renal tuberculosis, ureteral tumor, enlarged prostate gland projecting into the bladder, and not infrequently, a filling defect in the bladder from a tumor.

Cystoscopy. Positive identification of a tumor of the bladder is made usually by cystoscopic examination. With local anesthesia and aseptic technique a small instrument is passed into the bladder without causing discomfort. Inspection of the entire surface of the mucous membrane then is possible. Tumors may arise in any location, but the majority lie at or near the bladder base. Non-infiltrating tumors vary in appearance but nearly all are attached to the underlying mucous membrane by a slender pedicle. Some

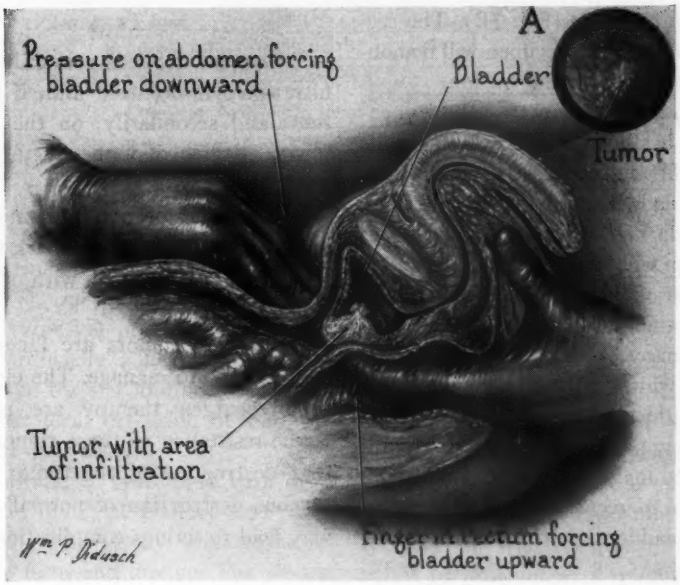

FIG. 8

are minute and others are large and almost fill the bladder.

Infiltrating tumors may have a thick, rigid pedicle, or they may be sessile. The surrounding bladder mucosa often is edematous and contains large blood vessels running towards the tumor. Ulceration of the growth is common and clots and calcareous material may adhere to its surface.

Biopsy. If the nature of the pathologic condition still remains in doubt, a small piece may be removed through the cystoscope with biopsy forceps. This procedure, however, may cause brisk bleeding, and it is wise to have a fulgurating electrode and surgical diathermy machine available so that an electric spark may be applied immediately to any bleeding points. In most cases in which biopsy is contemplated it is more satisfactory to have the patient in the hospital and under sodium pentothal anesthesia so that a really accurate evaluation of the whole situation can be made. Under these circumstances the resectoscope sheath is introduced and the projecting mass cut away (Fig. 7A). After these pieces have been washed out and placed in a specimen bottle, the portion of the mass within the bladder wall is scooped out and

TABLE 4

Bimanual Examination	Depth of Infiltration	Prospect for Cure
No thickening; no mass	Submucosal or superficial muscular (see biopsy)	Good
Thickening; no mass	Submucosal or superficial muscular (see biopsy)	Good
Mass, rubbery consistency, movable. Lateral ligaments negative	Deep muscular or perivesical (if not large papilloma; see biopsy)	Poor
Mass, stony consistency, movable. Lateral ligaments negative	Perivesical	Poor
Mass, stony consistency, movable. Ligament thickened and indurated	Perivesical	Very poor
Mass, stony consistency, fixed	Perivesical	Very poor

Jewett, H. J., in chapter on Neoplasms of Bladder, The Cyclopedia of Medicine, Surgery, Specialties; Philadelphia, F. A. Davis Company, 1950.

placed in a separate bottle (Fig. 7B). The sections made from the latter specimen will demonstrate roughly the extent of infiltration.

Bimanual Palpation. After the above-mentioned procedure has been concluded, and while the patient is still under anesthesia, bimanual palpation of the bladder wall is carried out (Fig. 8). The correlation of the biopsy findings with this examination will indicate the prognosis with a fair degree of reliability (Table 4), provided 1) the treatment subsequently employed is sufficient to remove or destroy all the cells of those tumors which are still completely localized to the bladder wall, and 2) the patient submits to regular, periodic cystoscopic examinations in order to make possible early identification and control of recurrences in other locations within the bladder.

Treatment

Treatment depends primarily on whether infiltration has occurred and, if so, to what extent; and secondarily, on the location, multiplicity, degree of malignancy, and size of the growth.

In the case of non-infiltrating tumors, the application of an electric spark through a cystoscope, or the removal with the resectoscope, usually suffices (Fig. 9).

Infiltrating tumors are far more dangerous and difficult to manage. The electric spark and deep roentgen therapy are rarely adequate. Radio-resistance of these tumors is so marked that destruction of the tumor involves simultaneous destruction of normal tissue, and this may lead to serious complications.

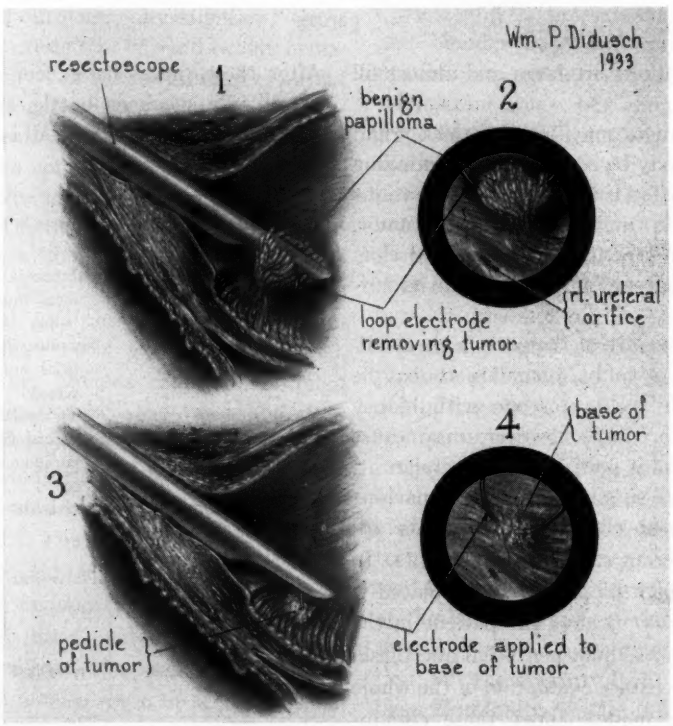

Fig. 9. Jewett, H. J., in chapter on Neoplasms of Bladder, The Cyclopedia of Medicine, Surgery, Specialties; Philadelphia, F. A. Davis Company, 1950 (courtesy of Dr. Robert W. McKay, Charlotte, North Carolina).

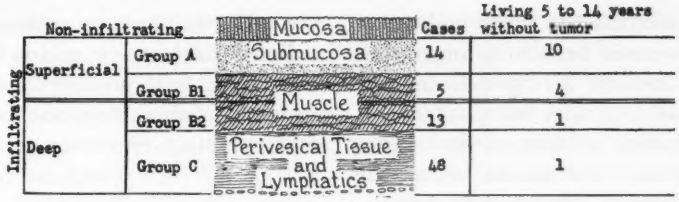

FIG. 10

Removal sometimes is possible with the resectoscope (Fig. 7), but if massive invasion is present a more extensive procedure usually is required. This ordinarily takes one of three forms depending on the size and position of the mass and whether local extension beyond the bladder wall is demonstrable.

The first is suprapubic cystotomy with deep excavation of the involved bladder wall with the cutting loop, followed by application of radon in suitable form and dosage. The second is partial cystectomy, especially when the infiltrating mass occupies a freely movable part of the bladder. The third is total removal of the bladder accompanied by appropriate diversion of the urinary stream. Simple total cytsectomy at present seems indicated for palliation when nothing else will suffice, and for possible cure when thorough conservative treatment has been followed by a contracted, irritable bladder with widespread recurrence within it.

The results in 80 cases treated by the last 2 methods are indicated in Figure 10. It seems evident that in general little can be expected when the infiltration has passed beyond the halfway level in the muscularis. For this reason it is important to classify each tumor before operation according to whether it is superficially or deeply infiltrating (Table 4).

Tumors that are superficially infiltrating usually are still localized. At present these seem to be treated best by excavation with the loop, with or without radon depending on their extent, when they occupy the more fixed portions of the bladder, and by partial cystectomy when they occupy the vertex or the superior portions of the anterior, lateral, and posterior walls. The latter method of treatment for tumors in this group provides a 5-year survival rate of 83 per cent.

Tumors which have extended more than halfway through the muscularis usually are no longer localized. The 5-year survival rate after partial cystectomy (segmental resection) is 3 per cent, and after simple cystectomy, 10 per cent. Figures for survival rate after radical cystectomy, in which regional lymph nodes and pelvic peritoneum were removed with the bladder, with and without pelvic exenteration, indicate that the salvage rate is not increased appreciably by these more extensive procedures, although an occasional patient may be cured only by these methods (Whitmore and Marshall, 1955). Only one of 32 patients reported by Whitmore and Marshall whose retroperitoneal lymph nodes were involved lived 4 years after radical cystectomy and exenteration.

At the moment it seems that a cure by any method is unlikely when the tumor has reached the perivesical fat and especially when local extension beyond the bladder wall can be demonstrated. In the latter event it would seem better to be content with palliative intervention when practicable (electroexcision and radium, partial cystectomy, or even simple cystectomy if absolutely necessary), and help to make it possible for the patient to live with his disease. This appears to be the only alternative to an extensive pelvic dissection (radical cystectomy with or without exenteration) with a low incidence of cure and with the prospect of great risk and subsequent disability.

In summary then, the most gratifying results

are obtained in those cases in which infiltration either has not occurred or is only superficial. Early diagnosis therefore is of paramount importance. Hematuria, gross or microscopic, and frequency of urination without obvious cause are merely symptoms and should be neither disregarded nor treated, but properly investigated. If a satisfactory explanation is not immediately forthcoming, cystoscopy is indicated, so that the least possible delay will occur in making a definitive diagnosis, and in proceeding with appropriate treatment.

The Johns Hopkins Hospital
Baltimore 5, Maryland

PANEL DISCUSSION

Introduction

HARRY F. KLINEFELTER, JR., M.D.

One of the most important things Dr. Brown has done is to focus the interest and attention of doctors on the problem of rheumatic disease. Dr. Brown has been interested in rheumatic diseases for twenty years. He is a graduate of The Johns Hopkins Medical School, a former resident in medicine at Hopkins, and started the Arthritis Clinic at Mount Alto. He was in charge of VA research in that disease field when he accepted the chairmanship of the Department of Medicine at The George Washington University in 1948.

THE PUZZLING PROBLEM OF THE RHEUMATIC DISEASES*

THOMAS McP. BROWN, M.D.†

The invitation to speak in Baltimore this evening, and to describe our studies relating to the basic mechanism of rheumatic diseases, was received with considerable pleasure and also certain misgivings. The honor was of course greatly appreciated, particularly as much of the background for this work was developed at the Johns Hopkins Hospital. Furthermore, it was here that such outstanding medical men as Longcope, Hamman, Tillett, Rich, J. Howard Brown and others inspired so many of us to continue the search for a basic understanding of unexplained medical problems. Although there is good reason to believe that light is at last beginning to dawn in this dark sphere of the rheumatic diseases, one realizes his great inadequacies in attempting to discuss this mammoth problem. In this field we are not only dealing with one of the most highly controversial areas in all medicine, but we are also faced with the problem of integrating the many different facets which must be considered in order to obtain an understanding of the whole.

There are many research directions which investigators are taking, including improved tests in diagnosis, new methods of therapy particularly in relation to the steroid hormones, and studies of collagen and fibrinoid. At the present time, with the exception of rheumatic fever, few believe that infection plays a significant role in the major rheumatic and arthritic

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† Professor of Medicine and Chairman of the Medical Department, The George Washington University School of Medicine.

diseases. If the answers are to be found in the areas of greatest research support, we must focus our attention almost entirely on the fields of endocrinology, metabolism, and biochemistry. With the exception of Rich, whose work strongly suggests that hypersensitivity is basic in the rheumatic process, and Selye's general adaptation syndrome, no positive views have been expressed which might serve as a starting point for an attempted explanation of the puzzling clinical behavior of the rheumatic diseases.

Our own approach has always been in one main direction, namely, a pursuit of an understanding of the basic mechanism which produces chronic rheumatic activity. We have utilized to the fullest extent expressions of clinical behavior to gain ideas for laboratory investigation. When laboratory findings have been fruitful, these findings have in turn been reapplied to the patient problem. Certain facts have emerged from this effort over the past twenty years which have gradually suggested to us a new total concept of basic mechanism of the rheumatic diseases. This concept has proven useful to us in not only explaining why certain current therapeutic methods have failed, but in pointing the way to a new effective approach in treatment which could not have been found otherwise. At the present time the most valuable aspect of this concept has been to provide logical reasons for the heretofore unexplained clinical behavior and interrelationship of the various rheumatic diseases.

Background

Our research interest in this problem began in 1935 with an attempt to collect and analyze many of the clinical facts regarding the natural history and behavior not only of the rheumatic diseases but of all conditions where the major insult appeared to be in the connective tissue area. We have continuously added to these basic data as time has passed and in recent years have gained much new information by observing the behavior of these conditions in relation to various newer therapeutic approaches. In analyzing our clinical observations we have been impressed by the blending and overlapping of these many conditions: for example, the similarity of the nodules in both rheumatic fever and rheumatoid arthritis, the fact that mitral valvulitis can occur in rheumatoid arthritis and be similar in many respects to that seen in rheumatic fever or the carditis in glomerular nephritis. Many of the vascular changes in scleroderma, lupus erythematosus, rheumatic fever, and rheumatoid arthritis although different in degree, extent or localization present similarities in histological appearance. We have also studied the fluctuations and seasonal variations of all connective tissue disorders and have noted the many factors which seem to influence all these conditions in approximately the same manner such as psychological and physical stress, trauma, poor nutrition, exposure to cold, and infection. Certain major inconsistencies have required explanation. One of these which particularly interested us has been the sameness of the cardiac lesion in both rheumatic fever and Sydenham's chorea, whereas the streptococcal relationship exists with only one of these two conditions, namely, acute rheumatic fever. On the basis of the points of similarity it was logical to suggest that some unknown common denominator was present in all these conditions which, if found, might provide the key to the complex problem as a whole.

In 1935, when these views were discussed with associates and colleagues, little interest was shown. This may have been due primarily to the emphasis at that time on new diagnostic tests which unfortunately provided inadequate information regarding cellular behavior and were concerned primarily with humoral reflections. This approach served to separate further rather than to unite the various types of rheumatic disease. The elevated anti-streptolysin titer in acute rheumatic fever and glomerular nephritis placed these conditions in a unique category. There was a tendency to

minimize the pathologic similarity of rheumatic lesions and those observed in known hypersensitivity reactions because of the sharp differences in clinical behavior. It has been gratifying to note, particularly since the advent of cortisone, that there is at present a far greater tendency to draw together than to dissociate the rheumatic diseases. An example of the former trend toward clinical dissociation was the original attempt to place the rheumatic entity of palindromic rheumatism in a separate category from other rheumatic disorders. This condition is now considered to be a variant of rheumatoid disease. For many years Marie-Strumpell spondylitis and rheumatoid arthritis were considered to be fundamentally different diseases by many observers. Most investigators at the present time would place these two conditions in the same general category regardless of their very different clinical behavior. It has been this matter of synthesis and comparison upon which our research objective, a concept of mechanistic behavior, has been based.

Development of a Research Approach

The associated role of infection in rheumatic diseases has previously held a prominent position in the search for the cause of these conditions. There have been periodic cycles of interest and disinterest in this approach throughout the years. Following the last unsuccessful attempt to associate streptococcal infection with the mechanism of rheumatoid arthritis there has been a trend toward a metabolic explanation, particularly in recent years. There has been a general acceptance of the streptococcal etiology of rheumatic fever. The reduction of the incidence of rheumatic fever with the prophylactic use of sulfonamides and penicillin has provided strong support for this view. Several facts regarding rheumatic fever require further explanation however. How may we account for the continued smoldering rheumatic activity when all signs of streptococcal infection have passed? Why should some patients develop late manifestations of mitral stenosis without histories of rheumatic fever or symptoms suggestive of streptococcal infections? Why should there be such a high incidence of Aschoff bodies in the myocardium in clinically inactive rheumatic heart disease as revealed in pathological studies associated with the mitral commissurotomy operations? Exacerbations of acute rheumatic fever in patients who have been clinically inactive for years have been noted directly after mitral commissurotomy operations. Why have these attacks developed in spite of the complete absence of any signs of streptococcal infection? These highly important unanswered questions have suggested to us that there is an additional aspect in rheumatic fever which is non-streptococcal in the usual sense.

All present evidence points to the fact that rheumatic fever in the acute phase is an expression of hypersensitivity to streptococcal antigen. In the smouldering non-streptococcal late phase it would be logical to conclude that hypersensitivity also plays a basic pathogenic role. Continued chronic activity in all rheumatic diseases suggests persistence of an antigen or antigens, and the question must arise as to the nature of such persistent antigens. There have been two main approaches to this problem. One approach, thus far used mainly in the study of chronic glomerulonephritis, has been the investigation of the possible importance of auto-antibodies, which might be responsible for continued disease activity. We ourselves have been interested particularly in studies to determine whether or not the persistent antigen in rheumatic diseases may be derived from a microbial source. Bacteria have never been visualized in rheumatic lesions, and if we are dealing with a living antigen such antigen could not be bacterial but rather a virus or virus-like organism. We considered the analogy with swine influenza where a bacterium and a virus were both important in the pathogenesis of that disease. We then wondered if a virus-type component might not provide the best explanation for the non-strepto-

coccal phase of chronic rheumatic fever. Such an additional agent might also explain the non-streptococcal rheumatic aspects of Sydenham's chorea, and in a broader sense supply the missing common denominator in all rheumatic diseases.

In 1937, the speaker began a study of rheumatic fever from the virus point of view in the laboratories of Dr. Homer Swift. The chorio-allantoic membranes of embryonated hens' eggs were inoculated with exudates and tissue from patients with acute rheumatic fever, and control material was used from non-rheumatic subjects. During the first several months of this study no lesions appeared on these membranes following serial transfer studies of this material. Finally, when the blood or serum of rheumatic subjects was employed for inoculation we observed the development of large, tapioca-like lesions on some of the membranes and generalized thickening and edema of others without specific localized nodules. The nodular lesions appeared to develop in the mesodermal layer of these membranes. These lesions could be serially reproduced at will on chorio-allantoic membranes as long as the diluent contained human serum. Blind passage cultures in cell-free media inoculated with filtered material derived from these altered membranes, though failing to produce visible growth on the artificial culture media, would produce the same lesions on the chorio-allantoic membrane following inoculation. Sections of the membranes failed to reveal inclusion bodies such as those found in certain virus diseases, or any visible microbial forms. At first we concluded that we were dealing with a filtrable virus, but we could not explain the ability of this agent to propagate on artificial cell-free media. This fact would exclude it from the true virus category.[10] At approximately the same time Dr. Albert Sabin recovered a filtrable organism from the brain of a mouse, which he described as belonging to the group of pleuropneumonia-like organisms first described by Klieneberger in 1935.[1] This organism produced arthritis in inoculated mice. Pleuropneumonia-like organisms although similar to viruses in their filter passing property, differed in their ability to multiply in cell-free serum containing media. It will be recalled that serum had been found essential in the production of the tapioca-like lesions on the membranes. Our agent, therefore, had two of the characteristics associated with the pleuropneumonia-like organisms namely that it was filter-passing and that it could be carried on artificial media and on the chorio-allantoic membranes as long as serum was present. It differed from animal strains in that it produced no visible growth in broth. The characteristic microscopic colonies which Sabin had described were indecisive with our strains. Nevertheless we did conclude that the agent isolated from rheumatic fever patients was a member of the group of pleuropneumonia-like organisms. Unfortunately at that time little was known concerning the difference between human pleuropneumonia-like organisms and those of animal origin. It is now realized that the isolation of human strains is far more difficult than that of animal strains. We now know, for example, that the human strains do not cloud broth media. Sabin and Swift, both of whom were prominent authorities, soon concluded that our findings were of no significance. Had it been realized at that time that there were such great differences between animal and human strains, it is probable that interest in this approach would have been sustained.

In 1946 MacNeal and his associates[2] described an agent isolated from the blood and exudates of patients with acute rheumatic fever which they designated as a rheumatic virus. They mentioned thickening of the chorio-allantoic membrane as well as nodules in some of the membranes. The description of these lesions was similar to those which we had described in 1939 and which had been induced by the same method.

In view of some of our more recent findings

which will be discussed, it would appear important to us that this entire work be re-investigated. It has been observed that there is one distinctive method for the separation of true viruses and pleuropneumonia-like organisms. It is known that no true viruses are affected by any of the usual antibiotics or chemical agents which have an antimicrobial action.[8] Pleuropneumonia-like organisms or L organisms, as they are often referred to, are susceptible to some of these newer agents. Furthermore, there is a differential effect, some agents being more potent than others, and two antimicrobial substances, penicillin and sulfonamides, have no effect on the L organism. This selective action may prove useful as a means of suggestive identification in instances where tissue lesions occur as a result of an unknown invisible transmissible agent. As previously stated, the only known transmissible filter-passing, tissue-invisible agents are L organisms and viruses. It is likely that a number of L strains require a period of adaptation before they can survive on cell-free media. It is logical that some strains may never achieve this transition and would appear always as true viruses except for the important difference of their susceptibility to certain anti-microbial substances. At the present time the only method for positive identification of L organisms is limited to the observation of typical microscopic colonies and transition forms on specially prepared agar plates. Even those strains that have become fully adapted may fail to grow when minute alterations in the media occur. We have always realized that in order to determine the significance of these organisms, attempts to isolate them directly from the patients must be continued with the constant effort to learn more of their growth requirements and thereby improve the media used for their cultivation.

Pleuropneumonia-like Organisms, L Variants of Bacteria

In 1939 we continued this approach here in Baltimore and began the attempt to isolate L organisms directly from rheumatic exudates, blood and tissues. In the course of this work we obtained a culture of Streptobacillus moniliformis from the joint fluid of one of our patients with arthritis. This case proved to be an instance of rat-bite fever due to this organism.

As cultures of Streptobacillus moniliformis regularly produce two types of colonies, bacterial and pleuropneumonia-like colonies (L_1), the study of this organism bears a relationship to the subject discussed here today. Dr. John C. Nunemaker joined me to work on this problem for the next two years with the main objective to determine whether the L_1 was truly a derivative of the Streptobacillus moniliformis or a symbiont. Our findings confirmed the views of Dienes that the L_1 was a true bacterial variant. Since this time Klieneberger-Nobel who had discovered the L_1 form in 1935 has retracted her original contention that the L_1 was a symbiont, and now agrees that it is a true variant of the Streptobacillus. This seemingly academic fact has, we believe, great practical importance partly because of its significance in bacterial and infectious problems and partly because of its indirect bearing on the problem of the rheumatic diseases. The Streptobacillus-L variant relationship is considered to be a prototype of a similar phenomenon now known to occur with many common bacteria. It is not within the scope of this talk, to discuss the interesting problem of the relationship of apparently independent pleuropneumonia-like forms to those originating from bacteria. For brevity's sake we will refer to all pleuropneumonia-like organisms regardless of origin as L organisms.

Early in the course of studies on this new group of organisms it was found that they were resistant to sulfonamide drugs. Dr. Guy Hayes and the speaker developed a simple method for isolating L organisms derived from the Gonococcus by adding sulfonamide drugs to the culture media. By this means the sulfonamide sensitive gonococcus was killed and the sulfonamide resistant L organisms remained in pure

culture. Dienes has since extended this method and has found that penicillin actually promotes the rapid transition of L forms from other bacteria. A number of Gram negative organisms, such as colon bacillus, Proteus bacillus, Neisseria, influenza bacillus, Bacteroides, and the typhoid bacillus were the first to reveal this tendency to produce L forms. Dr. Dienes has indicated that there is reason to believe that all bacteria will eventually be shown to have this ability to promote the formation of L organisms and it is of particular interest that Sharp has recently demonstrated that Beta hemolytic streptococci are capable of producing these L forms[4]. It is well to point out that once the L organism has split from its parent form, these L variants now form a new group of microbial agents entirely different from the parent (morphologically, culturally and possibly in their pathogenic properties) but morphologically and culturally similar to each other. When growing in colony forms they are unique in their minute size and have a dark reticulated center which burrows into the agar and a very superficial lacy peripheral zone which is easily disrupted by physical means. This important microbiological fact, namely the L-splitting phenomenon, was not accepted for a number of years after Dienes's original observation, but it has now been amply confirmed. Furthermore Dienes and his coworkers have provided evidence that the L-splitting phenomenon can occur in tissues, and it is also likely that these organisms are harbored intracellularly in a manner comparable to that of viruses.

Many of the animal strains are pathogenic for animals, but this pathogenicity is highly species specific. Rat strains will not infect mice, and strains isolated from cattle and sheep also behave in a highly species specific manner. It is not surprising, therefore, that the human strains do not produce disease in laboratory animals. This adds to the problem of determining their pathogenic significance in man.

Laboratory and Clinical Correlation

In 1942, our work, which had been gaining considerable momentum, had to be abandoned until early in 1946 because of the war. During that time Dr. Dienes had continued his studies and made additional important contributions. On returning we found to our great disappointment that the strains which we had collected and frozen prior to the war had been lost and furthermore, that there was very little interest in the subject as most investigators had concluded that it had no practical bearing on the problem of rheumatic diseases. We were then faced with either abandoning this work or starting over again, and we chose the latter.

We found that rheumatoid arthritis was becoming a great problem in the Veterans Administration, principally because of the influx of new veterans with this condition and the number of hospital beds already filled with veterans from other wars who had chronic rheumatoid and other forms of arthritis. Dr. Paul B. Magnuson was very anxious to start a program of research and rehabilitation in this field, and we were given the opportunity to organize this program and to carry on our work in research and rehabilitation through the formation of an arthritis research unit at the Veterans Administration Hospital in Washington, D. C. Dr. Ruth Wichelhausen was made director of the laboratory and Mrs. Lucille Robinson our research bacteriologist. An arthritis clinic was established which assured long-term follow-up studies and a planned attack on the disease from a combined fundamental, therapeutic and rehabilitation point of view. Since 1948 when the speaker moved to the George Washington University Hospital where we established another arthritis clinic, our group has grown to include Dr. Stewart Bush and Dr. William Felts, who are conducting clinical investigations, and Dr. Harold Clark, a biochemist, as well as several technical assistants. We have recently opened a new arthritis research laboratory at the George Washington University Hospital

which will greatly augment our joint research effort.

When we began this new program in 1946 it was apparent that a possible L organism relationship to rheumatic diseases could neither be established nor denied by the direct culture method alone. We had had evidence from the inability to maintain growth of some freshly isolated L strains that strains could exist in tissues which would not grow on artificial media, and their presence would thereby escape attention. We therefore sought some indirect method to attack this problem. Aureomycin had been found to be effective on L organisms isolated from a case of nonspecific urethritis as well as on other strains. We soon observed that this drug eliminated these organisms in vivo from the genital tracts of patients with a variety of rheumatic conditions. Soon one of our most valuable clues presented itself. It was observed that an exacerbation of rheumatic symptoms was often associated with the administration of aureomycin. Such flare reactions were most marked during the early phase of treatment with this drug. This reaction to aureomycin was similar to and often more severe than that observed with gold salts when employed in the treatment of rheumatoid arthritis. As both of these chemically unrelated drugs possessed the property of being effective against L organisms in vitro, it was logical to consider that the substrate which was affected specifically in rheumatoid tissues was also the L organism. This observation also suggested that the induced flare reaction was a form of hypersensitivity reaction resulting from the release of antigen derived from the chemically destroyed L organisms. One could liken this reaction to the Herxheimer phenomenon in syphilis or the flare in brucellosis induced by certain antibiotics. Both syphilis and brucellosis are associated with a high degree of tissue hypersensitivity. It was soon found that terramycin was more effective than aureomycin against the L organisms in vitro, and in vivo there was also a parallelism. When both drugs were given independently to the same patient and in the same dosage, the more potent anti-L substance, terramycin, would produce the more marked flare reaction. By approaching this in another manner it was found that a dosage of 10 mgm. of terramycin would be comparable to 250 mgm. of aureomycin in producing flare reactions of the same intensity. With this knowledge another avenue of investigation was open to us. By keeping the dosage of terramycin low or by using the less potent anti-L substance aureomycin in slightly higher doses, it would be theoretically possible to gradually remove the L organisms from the tissues without causing major clinical exacerbations. If these agents were truly present and responsible for the hypersensitivity reaction, long term low dosage therapy should result in clinical improvement in our patients. We recognized that we were not dealing with an ordinary infectious problem where bacterial invasion was the prominent feature. Rather we were faced with a situation where the pathophysiological alterations were apparently produced by reaction to infection. Thus the host reaction was as important in pathogenesis as the parasite itself.

Another observation which intensified our interest was made at this time. Those patients who had been given a much larger dosage of these antibiotics and in whom a constitutional flare reaction was induced were found to exhibit coincidental elevation in sedimentation rate, gamma globulin as well as total globulin and a fall in serum albumin and hematocrit. This suggested that a toxic substance had been released at the time of the induced intensification of their smouldering hypersensitivity reaction. When cortisone was employed in conjunction with the antibiotics, such flare reactions either did not occur or were modified and chemical worsening of the hematological picture was not noticeable until much larger dosages of the antibiotics were given. This interference phenomenon with cortisone suggested to us that

this drug modified a probable hypersensitivity reaction in some manner, possibly at the antigen-antibody level, possibly by affecting substances produced by union of antigen and antibody, or by affecting the reactivity of host tissues.

Certain clinical facts also became apparent to us as we pursued this work. Those patients who exhibited low hematocrit and serum albumin levels and high globulin levels prior to treatment had the most intense flare on a given dosage of the antibiotic. Improvement in the blood picture, primarily in the hematocrit and serum albumin, correlated well with clinical improvement. The first clinical changes to occur were those of lessening of the duration of morning stiffness, a very characteristic feature of all rheumatic diseases. Those patients who would require four hours to "limber up" to the point where they could move around would now take two hours or less although the initial intensity of discomfort on awakening would be the same. In many patients under long term management the morning stiffness has disappeared. Another early sign of improvement has been the appearance of short periods of a feeling of well being lasting initially for only a few hours but later persisting for several days. "Bad days" have been progressively less frequent with the passage of time but when they have appeared the symptoms have often been as severe as ever. General improvement often has been noted, usually prior to joint improvement. The untreated arthritic can never be certain of the duration of a given exacerbation whereas the patient under treatment has learned the expected cycles of his flares and their anticipated duration. Through this understanding he has gained a sense of confidence and hope, which has distinct therapeutic value. He has learned to treat the flares with simple remedies such as salicylates, local heat and rest. It has been found important to teach the patient to live with the variables of his disease and not to insist on the necessity of strong pain relievers such as narcotics or steroids.

We have paid considerable attention to the psychological reactions of the arthritis patient during the various phases of his illness. These patients usually have many psychological abnormalities most of which have been deep and fixed. Many of these feelings have been directed toward the medical profession itself. Some patients have become particularly bitter toward those who have indicated that their trouble stemmed from their own personality defects. Those who have escaped from the initial good effect of cortisone often vigorously condemn the physician who advised them to take cortisone. It is little wonder that they try so many useless remedies because of the obvious confusion in this field. The many areas of uncertainty and disagreement within the profession have served to deepen their resentments. These patients have also become very sensitive to their environment. With ordinary difficulties at home, such as the children becoming too noisy, they often have bursts of unreasonable anger for which they have no explanation. One of their most disturbing symptoms is a progressive worsening of memory, which neither they nor the physician have necessarily considered part of the disease itself. They have been frequently embarrassed by not being able to remember the names of old friends. Relief of these symptoms has been frequently more important to the patient in retrospect than the relief of pain. Loss of interest in matters which previously held their attention has also been a very distressing symptom of the rheumatic diseases. This symptom has been rationalized by the patient as an obvious result of the persistent painful and disturbing aspects of the disease, rather than a specific manifestation of the disease complex itself. With improvement there has been return of interest in their environment which has often been one of the most striking changes. A very distressing subjective symptom has been the sense of overwhelming

fatigue. This fatigue has been variable and has developed at unexpected moments. Often patients have planned an evening out with friends and then announced at the last moment that they could not go. They appeared quite well just prior to the time that these symptoms suddenly developed, and as a result they have left the impression of selfishness and lack of concern for the welfare and enjoyment of others. Family discussion and argument on these matters have led to deeper psychological disturbances of the patient and worsening of the symptoms. The patients who have suffered most from the lack of general understanding of their problem have been those with few objective changes. These patients frequently have had as great or greater psychological difficulties than those with marked objective alterations. The development of progressive, visible, pathological alterations which have revealed at least some apparent reason for their behavior has often been a welcome relief.

All the manifestations of the rheumatic diseases whether objective or subjective have been observed to react in a related manner to the anti-L substances. This effect has paralleled the dosage of a particular drug, and also the in vitro differential anti-L effectiveness of the various substances employed. A differential effect has been noted on the rheumatic spectrum as a whole, there being a marked difference in the effect on mixed rheumatoid and osteoarthritis at one end of the spectrum and lupus erythematosus at the other. In general those patients whose illness has reached the degree of severity to produce anemia, depression of the serum albumin, elevation of the total globulin and the gamma globulin, and marked elevation of the sedimentation rate, reflect a more intense reaction pattern to the anti-L substances than the "hematologically" milder cases. Large dosages of the anti-L substances given initially have worsened or flared any or all of the existing rheumatic manifestations. In many instances where the manifestations have been for the most part subclinical and subjective they have been brought to the surface and clearly defined with visible objective changes. A subjectively painful, but otherwise normal joint has become objectively swollen, hot and tender to a degree directly related to the dosage and anti-L potency of the particular preparation employed. Cortisone and other interfering substances have been found to modify or obliterate this medically induced flare reaction depending on the amount of the interfering substance employed and the relative potency and the dosage of the anti-L substance used. Those conditions which have exhibited the greatest degree of presumed hypersensitivity such as lupus erythematosus, malignant rheumatoid arthritis, rheumatic fever, periarteritis nodosa, psoriatic arthritis and ulcerative colitis may in the initial phase of treatment exhibit almost uniformly distinct and sometimes severe flare reactions from as little as 10 milligrams of terramycin every third day. Where the severity of the condition lessens, either from spontaneous improvement or as a result of the continued carefully titrated low dosage therapy, greater tolerance of the drug has been noted and larger dosages accepted without inducing an additional flare response. If, however, the dosage has been increased too rapidly at any time the initial marked worsening of the diseases in relation to the medication has been observed. There has appeared to be an age and sex difference in the tolerance of the anti-L substances in respect to this flare phenomenon. Children even with febrile forms of rheumatic diseases have appeared to accept the anti-L substances better than adults with the same type and degree of involvement. Flares have tended to be less intense and better tolerated in males than in females. The psychological manifestations in association with rheumatic diseases have appeared to react in the same manner as have the physical objective alterations and the hematological expressions. The symptoms of fatigue, tension, mental depression, and ex-

plosive unjustified anger worsen, as do migraine headaches, in direct relation to the potency and dosage of the anti-L drug. Constipation, a frequent associated feature in rheumatoid disease, has become more marked even while using a drug which is generally considered to have a tendency to produce loose bowel movements. Colitis when present in a rheumatic subject will exacerbate with anti-L therapy. We have also observed that rheumatic subjects who have associated active peptic ulcers may develop an aggravation of the ulcer symptoms even if the anti-L substance is administered parenterally. Because of the parallelism of the psychological and physical behavior in relation to the induced flare response, it has become progressively more apparent to us that the mental reaction has been an effect rather than a cause per se in the rheumatic complex. The ultimate clearing of the psychological expressions of the disease on continued long-term low-dosage titrated anti-L therapy, which has been paralleled by progressive hematological improvement, has provided additional support to this view.

A Concept of Mechanism

Sufficient background has now been given to indicate the facts which, when properly integrated, might allow us to derive a concept of mechanism. We have demonstrated, through a method of clinical testing, that the phenomenon of tissue hypersensitivity has appeared to be basic in the rheumatic mechanism. This view is compatible with the pathological interpretations and experimental findings of Rich and his associates[5] who have indicated that the mechanism of hypersensitivity is fundamental in all of the connective tissue diseases. Klinge, Swift and others have presented evidence that the mechanism of hypersensitivity is basic in rheumatic fever.

The effect of cortisone on rheumatoid disease bears a parallel to its effect on various allergic disorders. In the cortisone escape phenomenon, there is a gradual worsening of the condition following the sustained period of improvement in spite of maintenance or increase of the cortisone dosage. Cases have been reported where there is a transition from relatively benign rheumatoid disease into a malignant phase or into periarteritis nodosa during the period of cortisone therapy. This suggests that the antigen responsible for this reaction may have multiplied and disseminated and thus the cortisone barrier has been broken. The known tendency for infectious conditions such as tuberculosis, streptococcal and staphylococcal infections to spread during cortisone administration has in some regards presented an analogous situation. If the theoretical antigen has increased because of some cortisone produced interference with the basic immune mechanism in the rheumatoid subject, one might also expect progression of the disease. Mirick[11] has indicated that antibody continues to form during cortisone administration in immunized subjects. It is possible that antibody is rendered incapable of combining with antigen during the "block" period and that there occurs an accumulation of both antigen and antibody in the tissues, which becomes doubly apparent by the rebound phenomenon when this "block" is removed. The exact mechanism is, of course, a matter of conjecture at the present time. However, it might be agreed that all the points mentioned favor the view that hypersensitivity is basic. If one accepts this fact, the remainder of the argument falls into a logical pattern.

We have found that all the substances tested which effect L organisms in vitro have produced an effect on rheumatoid disease in manner which parallels the in vitro activity. We have also observed that cortisone, ACTH, and Butazolidin interfere with this effect in a manner which allows the anti-L substance to be raised to higher dosage without producing a flare reaction which would occur without them. In addition we have indicated that a point is reached where the "blocking effect" no longer holds.

When antigen of any type reacts with anti-

body in the tissues it is generally agreed that some irritating or toxic substance is formed. In allergic states such as urticaria, this substance is capable of causing sufficient capillary damage to allow fluid to escape from the small vessels and accumulate in the tissues with the production of the familiar urticarial wheal. In acute allergic reactions it is believed that histamine is one of the main substances elaborated, which has this irritating capacity. In chronic hypersensitivity reactions it is probable that histamine is far less important. Certainly antihistamine drugs have little if any effect in rheumatoid diseases, which parallels their failure in the bacterial hypersensitivity reaction of tuberculosis. The continuous or intermittent formation of the toxic resultant of a long standing antigen-antibody reaction might be expected to produce chronic irritation and subsequent tissue reactions of various types. The question which has come to mind is whether or not the irritating substance may be a proteolytic enzyme, formed or released from tissues by interaction of antigen and antibody. Such a mechanism has been postulated by Dubos in tuberculosis where bacterial hypersensitivity can be clearly demonstrated. In rheumatoid disease the reaction is located primarily in the connective tissue of the joint. This results in articular inflammation, unexplained local damage of cartilage, and bony and synovial alterations. Might not these changes be accounted for by a high concentration of a toxic substance in this location? It is of interest in this regard that some strains of pleuropneumonia-like organisms isolated from certain animals (sheep, rats, mice, and chickens) have been known to have a particular affinity for joint tissues. One could possibly explain the development of subcutaneous nodules on the basis of either localization of antigen and antibody at particular sites releasing the irritating substance locally, or by diffusion of this substance from some more distant focus. Diffusion might promote a general tendency for all tissues to react to injury in the same manner. This might account for the fibroid nodules occurring at points of pressure and the formation of calluses on the feet where pressure is greatest and most constant. It could also explain the increased capillary permeability and fragility, the tendency to bruise easily, the petechial hemorrhages and nose bleeds frequently observed in rheumatic subjects. The circulation of such toxic substance could produce anemia and depress serum albumin. We have indicated that when the induced disease exacerbation is at its maximum the hematocrit and albumin may be reduced in direct relationship to the intensification of this flare. The concomitant increase in mental depression, weakness and fatigue suggests that the same irritating substance released into the circulation from various sites, including the spleen and the reticulo-endothelial system in general, could also affect the central nervous system. It has been reported[6] that the injection of a small amount of human serum albumin often provides transient clinical relief similar to that of cortisone. We have been informed that albumin is an avid absorber of impurities, and because of this it may serve as an important transport mechanism for a toxic circulating substance. This would explain the temporary effect of unsaturated serum albumin and the nonspecific effect of whole blood. Enlargement of the liver frequently observed in rheumatoid arthritis might be explained by the great demands placed on this organ through the possible saturation of the available serum albumin. It has also been of interest that the point where improvement begins to appear following long-term low-dosage anti-L therapy is usually associated with a rise in serum albumin which precedes a fall in gamma globulin and sedimentation rate.

One of the unexplained facets of this puzzle has been the mechanism whereby as little as ten milligrams of terramycin administered by mouth can eliminate L-organisms from the prostatic or cervical secretion. This does not correlate with the less effective in vitro activity.[9]

One explanation for this might be that a few of the most sensitive organisms could be destroyed by this small amount of terramycin. The small amount of antigen thus released from an intracellular source might react with previously formed extracellular humoral or fixed tissue antibody to promote the production of a sufficient quantity of the "toxic substance" to be the main agent capable of destroying the L organism. To test this theory we administered both phenylbutazone and terramycin to a few patients from whom L organisms could be cultured, and observed that a ten to fifteen fold increase in terramycin was necessary in combination with Butazolidin to render cultures negative for L organisms. It appears therefore that phenylbutazone may act not only as an anti-inflammatory agent, but that it interferes with the in vivo elimination of L organisms. Further observations will be necessary to determine whether this is due to interference with the "toxic substance" discussed earlier and whether this substance is in fact antimicrobial. The toxic resultant of this antigen-antibody reaction, although an irritating, disease producing substance, may provide the important function of localizing, inhibiting and destroying the L organism. These very preliminary studies may provide a clue to the nature of the defense mechanism in the host. They suggest a possible link between the aspects of hypersensitivity and immunity. This could explain the consequences, which we must expect if we administer the anti-inflammatory steroid hormones alone in these conditions. On this basis it would be expected that the more potent the hormone the greater the likelihood of the ultimate worsening of the disease. The development of malignant rheumatoid disease and periarteritis which has been observed in steroid hormone treated patients would therefore be logically explained. The rapid progressive destructive changes in joints under cortisone therapy which have been observed by us as well as others would also be understood.

On the basis of this concept it has now been possible to visualize why the many seemingly unrelated types of medication employed in rheumatoid disease have an effect. Realizing the nature of the particular substances which have been employed, whether they be gold salts or antibiotics on the one hand, steroid hormones on the other, or physical measures such as x-ray therapy in a third instance, their logical place in this mechanism would seem apparent.

Substances which would affect the antigen: Achromycin, terramycin, aureomycin, chloramphenicol, streptomycin, gold salts, nitrogen mustard.

Substances which would either interfere with the antigen-antibody mechanism or the irritating resultant of this reaction or both: Cortisone, hydrocortisone, ACTH, Butazolidin, Doca and ascorbic acid, serum albumin, whole blood, postpartum plasma, salicylates.

Substances which would interfere with antibody: X-ray therapy, nitrogen mustard.

It has been of interest to us to review each new substance which has been described as effective in rheumatic diseases with the thought of the hypersensitivity mechanism in mind and to predict the ultimate success or failure of these substances. An example of this may be noted in our report in 1950[8] at the height of cortisone enthusiasm when we indicated that the steroid could not be expected to have a lasting effect on the course of this disease. This prediction of ultimate cortisone failure was possible because of the logical site of action of the hormone in this mechanism.[8] It is interesting to realize that the two substances which have withstood the test of time in rheumatoid disease, namely gold salts and salicylates, have mild action in their particular phases of activity according to this concept. Salicylates have been shown to affect antigen-antibody mechanisms, and gold salts have been shown to have an effect on the theoretical source of antigen, the L organism. Only those substances which finally eliminate

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the offending antigen could be expected to create a permanent remission in these cases according to this concept.

There is one final aspect of the mechanism, the significance of which we have just begun to realize. We have recognized that some of our cases who have not responded well to treatment have improved considerably when a hidden focus of infection was finally found and removed. A number of patients with dental infection which has been either overlooked or not suspected have responded better to the anti-L therapy when these foci have been properly treated. Others have had pelvic abnormalities, gall bladder disease, urinary tract or tonsillar infections which, when corrected, appeared to result in a more rapid recovery. The delay in recovery in the presence of hidden focal infection could be explained on the basis of the constant discharge of antigen from these foci derived from either remaining parent organisms or their L variants.

There have been other cases, however, who have presented a complete therapeutic dilemma. These patients have usually had symmetrical deformity, depression of hematocrit and serum albumin, high globulin and gamma globulin levels. Some of these patients have improved with cautious titration of anti-L substances. Others have flared regularly with any dosage of antibiotics which we have employed and have failed to show improvement. We have suspected in these cases parasitism of the reticulo-endothelial system, particularly in the spleen with or without obvious enlargement. The obscure nature of symmetrical deformity could be explained on this basis by the constant and uniform discharge of antigen or toxic substances or both from the spleen, causing a similar progressive effect on both sides of the body. The anemia and other pronounced blood disturbance would suggest a direct action on the blood elements from a readily accessible source such as the spleen. Splenectomy has been performed in rheumatoid disease in the past with inconsistent results. This would be expected when one considers that only one site of antigen concentration would be removed by splenectomy. In view of the fact, however, that the spleen is the most vascular organ in the body and in direct continuity with the circulation, it would be desirable to remove, if possible, such a site where released antigen would have direct access to the blood stream. One could visualize the consequences of continuous infinitesimal intravenous horse serum injections in an individual who was sensitized to horse serum. The same situation might obtain in rheumatoid disease with a different antigen. At the present time we have performed splenectomies on a selected small series of cases who had presented a therapeutic dilemma. The most interesting and consistent finding following the splenectomy has been the acceptance of larger doses of the antibiotics than those tolerated before the operation. This would suggest that a major antigenic source had been removed and that subsequent antigen release from other areas was more localized and less likely to enter the blood stream directly. We have been impressed with the preliminary observations from this study.

It might be of interest to mention briefly the case of a young man (D. M.) from this city whom many of you know and have followed with interest. He presented a very good example of this therapeutic dilemma. He came to us several years ago in a desperately ill condition with malignant rheumatoid arthritis and many features suggesting disseminated lupus erythematosus following the escape from cortisone therapy. When first seen there was fever, multiple destructive joint changes, marked anemia, low serum albumin, high globulin, greatly elevated sedimentation rate, and a weight loss of approximately 80 pounds. He had been forced to remain in bed much of the time. He was found to be highly sensitive to anti-L therapy (terramycin) but the drug was administered in titrated small doses and his tem-

perature eventually returned to normal. There was no improvement in his weight, however, and his joints remained severely and progressively involved. The anemia improved slightly. The sedimentation rate remained highly elevated. Following splenectomy, which was performed in the spring of 1953, there was no immediate improvement, and six months later, when his case was reviewed, he showed no signs of weight gain and joint activity was severe. It was found however that he could now tolerate larger intravenous antibiotic doses daily, without exhibiting flare reactions. During treatment his appetite improved and he ultimately regained the 80 pounds in weight. His blood findings have greatly improved and he is making rapid strides in general improvement and mobility in spite of severely damaged joints. It may be of interest that the two splenectomy cases in this small series, who have not done well, have been individuals with concomitant infection. One has had a urinary tract infection and another an infection in the pelvic region.

Discussion

This concept has enabled us to explain the many bizarre features of the behavior of rheumatic diseases for which no explanation has been provided in the past. This understanding has indirectly reinforced the validity of the concept itself. For example, an old observation which has never been explained has been the dangerous worsening of disseminated lupus erythematosus treated with small doses of gold salts, whereas improvement has been noted in discoid lupus with the same dosages of these drugs. The extreme degree of generalized sensitization of tissues in disseminated lupus compared to the localized discoid type would account for this difference in reaction to antigen released by gold salts. We have noted a complete parallel between the effect of the broad spectrum antibiotics and the chemically unrelated gold salts in their comparative action on disseminated as opposed to localized collagen disease. This concept has also provided an explanation for the stiffness, which the arthritic patient notices soon after arising in the morning. During sleep the toxic products of the antigen-antibody reaction would be expected to increase in concentration in the tissues and promote more muscle spasm and pain until motion was resumed and the irritating substances were mobilized. We can now explain the worsening of rheumatoid disease by excessive exercise or too vigorous physiotherapy. During such circumstances antigen could be released by being mechanically expressed from the cell, making it available in the extracellular space to react with antibody and thus increase the reaction. The importance of a balance between exercise and rest, which is fundamental in good management of the rheumatoid subject, is in keeping with this concept. We now have a reason for a high protein diet, particularly in less severe cases which would logically profit from a greater protein intake and more available albumin to interfere with the hypersensitivity reaction. An explanation for the psychological features of the disease such as cyclical mental depression, nervousness, anxiety and poor memory has been provided by the probability of intermittent vascular dissemination of the toxic resultant of the antigen-antibody reaction. This concept has provided a reason for the development of subcutaneous nodules and the many metabolic and hematologic alterations. It also places these abnormalities in a secondary rather than a primary position. In addition it accounts for the poor effect of hematinic agents in the attempt to correct the associated anemia when the basic disease producing factor remains unaltered. It is possible through this concept to integrate the various schools of thought into one pattern rather than to exclude one from the other, and the effect of the steroid hormones can now be explained on a logical basis. The selective effect of the various anti-L substances as reflected clinically in a graded antigen release expression, has suggested the presence of a specific sub-

strate, namely the L organism. The low dosages of anti-L substances found to be effective against L organisms in vivo have been well below the levels necessary to affect ordinary bacteria. Therefore the present concept should not be confused with the pathogenic considerations of a sensitivity reaction to ordinary bacterial antigen. This earlier concept has been considered invalid in the past, either because bacterial foci have not been present or, when they have been found, removal has not interrupted persistent rheumatic activity. A missing link has thus been provided through the concept of the L-variant of bacteria and the mechanism of hypersensitivity to the antigen produced which allows reconsideration of the discarded role of infection but from a totally different point of view.

It would be expected that the L-variant from a potentially virulent parent organism, such as the streptococcus, might create a more pronounced and dangerous form of hypersensitivity, such as rheumatic fever, than a possible L-variant of the colon bacillus from an antecedent pyelonephritis creating rheumatoid disease. The differences in clinical patterns of the many collagen disease types could therefore be explained on the basis of the differences of parent organisms from which the L-variant has been derived. In this total concept it also appears that an understanding of the host response is of significance equal to that of the parasite itself, and a comprehension of the mechanism requires precise clinical as well as fundamental knowledge. The introduction of the major thesis of hypersensitivity to L organisms in the human disease should minimize the objections stemming from the comparison with the obviously pyogenic, infectious arthritis of rats and mice due also to pleuropneumonia-like organisms. We have emphasized the strain differences encountered as well as species specificity. Unlike animal strains the human strains because of their minute size can neither be visualized in broth cultures or infected tissues. Furthermore the host differences in the rat and mouse compared to the human regarding hypersensitivity are well known. If the resultant of the antigen-antibody mechanism is an antimicrobial substance, we would have an explanation for the difficulty of culturing these organisms from areas where this reaction is intense, possibly accounting for another difference between the human and the animal diseases. This possibility might indicate an approach to better culture methods by neutralization of this tissue substance prior to cultivation.

From this concept a totally different, and we believe far more hopeful, therapeutic approach has arisen. In rheumatoid disease low dosage antibiotic therapy beginning in some cases with dosages of 10 milligrams every three days and gradually increasing the dosage according to tolerance, until levels have been reached of 50 milligrams or more every third day or every other day have proven effective. In some cases intermittent short courses of larger doses of antibiotics when ultimately accepted without producing flare reactions have proven useful. The improvement has usually been very slow, taking many months or even years for the achievement of a state of apparently fixed clinical and "hematological" remission. Once this point has been reached, medication has been discontinued, and if there has been a tendency to relapse, short courses of the same type of treatment have sufficed to control the disease completely. These low doses of long continued antibiotic therapy have not created bacterial resistance in the normal bacterial flora in the intestinal tracts of our patients thus far examined. Also in preliminary studies in our laboratory it has not been possible with the strains of human L organisms under observation to create in vitro resistance to the antibiotics employed.

Marked ultimate improvement in general well-being noted with this method of therapy has emphasized the total constitutional aspect of these diseases and the incorrectness of the frequent practice of directing attention almost exclusively to the joints. The more severe cases

in some instances have posed an additional problem of the use of an interfering substance, such as cortisone, other steroids or serum albumin, while attempts are being made to remove the antigen. If "blocking agents" must be employed, the dosage should be kept at a minimum level and used only when salicylates do not suffice. In very severe cases we have found that splenectomy may be useful. Such cases represent a small group of therapeutic failures in a large number of otherwise successful cases. The details of this clinical management of patients using this approach to therapy must await five year studies, before a valid report of effectiveness can be made. It is gratifying, however, that the interest in this mechanistic approach is becoming more widespread, and confirmations of our preliminary observations are being reported to us.

Conclusion

An attempt has been made to explain the basic mechanism of action of rheumatic conditions and to provide a logical reason for the clinical behavior of these diseases. A concept has been presented, which has been useful in directing our thinking toward the objective of the creation of permanent remission in these diseases. We can now visualize for the first time the likelihood that it will be ultimately possible to eliminate the cause of rheumatic activity. We have indicated a research direction, which in our opinion must be followed to achieve this end. We recognize that our own research effort represents only a bare beginning in this new direction, and that years of fundamental research will be necessary to establish these views.

May we conclude these remarks on a philosophical note. You have observed that we have utilized the methods of logic to the fullest extent. Logic is the foundation of both the scientific method and philosophy. In this field which has resisted basic understanding for 1500 years it is our belief that both logic and philosophy are important for the achievement of an ultimate solution. The ideas for the development of this concept have been based on fact. The explanation and interpretation of the behavior of the rheumatic diseases have been reached from logical deductions derived from this data and are not conclusive. Many of these thoughts were expressed here this evening with the desire to stimulate interest in basic research along these lines. It has been hoped also that these ideas may promote a greater realization of the importance of a more fundamental approach to the management of the individual patient.

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DISCUSSION

CHARLES W. WAINWRIGHT, M.D.* Mr. President, Ladies and Gentlemen, I have listened to a very delightful discussion by a skillful and eminent microbiologist and immunologist, and it is presumptuous for me to even attempt to discuss his paper. There are, however, certain things that arise in my mind as I hear him speak and read his writings, which continue to puzzle me.

Dr. Brown chose as his title tonight, The Puzzling Problem of the Rheumatic Diseases, and those words were certainly well chosen because the subject continues a puzzle and continues to baffle. He suggests an unusual form of hypersensitivity as the basic mechanism in rheumatoid arthritis and I think the matter of hypersensitivity has been in the minds of investigators of this disease for a long time. However, most of the reasoning is by analogy; bits of evidence come to light which tend to lend support to one view or another and there is always lacking some fundamental and important evidence to complete the chain.

The thing which has persisted in spite of all the efforts to solve this problem has been the fact that we have never really been able to produce the disease, and what is more important, never been able to reproduce the characteristic course of rheumatoid arthritis. Acute lesions can be produced in a variety of ways and have been, and only yesterday in Washington, a paper was read in which lesions which were similar if not identical with those of the acute phase of the rheumatoid joints were produced by a delayed tuberculin-like hypersensitivity.

Of course among the first, and Dr. Brown alluded to this in connection with rheumatic fever, among the first of bacteria thought to be incriminated in the disease was the hemolytic streptococcus, and there seemed to be considerable evidence that actually the bacteria were present in the inflamed joint. As you know they were reported as cultured from the blood stream, and to a lesser extent from the joints of many of those afflicted with rheumatoid arthritis. The fallacy in that work was later recognized and it was withdrawn.

Now Dr. Brown suggests a more fundamental antigen as the common denominator for all collagen diseases. I have long held the view that these diseases were closely allied if not intimately related, and it has been at least clarifying to some extent in my thinking about them, to feel that any rheumatoid arthritic was a potential disseminated collagen disease and why it was confined to the joints I am unable to say. Certainly the possibility of dissemination seems to be ever present. As Dr. Brown has alluded to, it does seem that in the last few years dissemination has been more widespread than formerly. To what this is due I would not venture to guess, but some feel that even steroids may play a part in this apparent tendency.

Dr. Brown, as he told you, showed many years ago here in Baltimore the presence of these "L" organisms, the group of organisms which he now brings to the fore, in both normal and in rheumatoid arthritic patients, and I was apparently under a false impression. My first impression was that the "L" organism would not be killed by gold but that the animal would be protected if gold was used prophylactically or at the time of the inoculation with "L" organisms and the production of a joint containing "L" organisms would be prevented. As I understand it now, these organisms are destroyed by antibiotics, and if that is true, one would expect a subsidence and a permanent subsidence of the joint reaction or the connective tissue reaction with the exhaustion of the antigen. That brings us to the major stumbling block in the whole proposition and that is, that this disease is subject to spontaneous remissions. That is the most characteristic thing of rheumatoid arthritis. It is perhaps more easy to understand the recurrence of the disease if the antigen reappears, but if there is a total destruction of the antigen, I think it would be reasonable to expect that the disease could be brought to a permanent conclusion.

So far as the treatment is concerned, it falls really into two categories. A trial and error method in which many agents are employed, most of which have proved ineffective, whereas some have altered the course of the disease. And in the second place, the pursuing of a type of therapy based on some given concept of the disease. In being able to influence the disease by any agent, we would hope that

* Associate Professor of Medicine, The Johns Hopkins University.

we could reason backward and thereby arrive at the mechanism in the production of the disease. However, that has been exceedingly difficult to accomplish. In using any agent which is effective, we have to always bear in mind the question of the spontaneous remission and we have to produce the remission with the agent with a consistent pattern and with sufficient regularity and frequency to carry it beyond the realm of spontaneous remission.

The matter of the effect of cortisone, I won't discuss because I really don't feel qualified to discuss it, but at the same time I must say that I share Dr. Brown's view with regard to cortisone, that any efforts to make it a means of therapy in the treatment of rheumatoid arthritis, if not the method of choice, is a very unwise procedure. We are, I think, very grateful to Dr. Brown for his discussion this evening.

Nine East Chase Street
Baltimore 2, Maryland

THEODORE E. WOODWARD, M.D.* Mr. Chairman, I welcome this opportunity to discuss Dr. Brown's very stimulating paper and will read my comments in order to conserve time.

Dr. Brown has called attention to the self-perpetuating nature of a number of microorganisms in the host, such as the pleuropneumonia groups which behave like viral agents.

There are similar syndromes in which the host does not succeed in eradicating the offending agent, i.e.: typhoid bacilli and the typhoid carrier state, brucellae as Dr. Brown mentioned, typhus rickettsia and its related Brill's disease.

Dr. Brown has called attention to the importance of the host and his reaction to injury and has defined the nature of the insulting antigen. He and his group are attempting to explore why defenses fail in response to certain antigenic stimuli and propose failure of immune mechanisms and other factors.

Dr. Brown, can we not extend your concepts and propose tissue deficiencies which are self-perpetuating after the stimulus has subsided and that future research will require definition of these deficiencies other than cortisone, etc.

There are a number of areas in which these ideas are finding application, i.e.: folic acid deficiency in the field of certain blood dyscrasias; the role of iron in the production of diphtheria toxin or the relationship of anaerobic conditions and the production of other toxins. Consider our knowledge of plague. It is possible to treat a patient with pneumonic plague with antibiotics which successfully eradicate the causative bacillus and yet death ensues if the specific therapy has not been given prior to the 20th hour of illness. We do not know the nature of these irreversible changes.

Are you not emphasizing, Dr. Brown, a very penetrating concept? Are you not asking in essence: what is toxicity, how do disease processes damage tissues, why do people die? Why do tissues of certain individuals such as arthritic patients continue to react unfavorably? You propose bacterial or viral variants or mutants, which conventional laboratory tools are not yet sensitive enough to detect. Is it an enzyme as you have suggested or an abnormal globulin?

You desire to probe into the tissue cell with a telescopic lens and a Warburg apparatus. Certainly Dr. Brown's concepts will find application, even though as he indicated a few may have to be cast aside through analytical trial and error.

May I ask, Dr. Brown, whether you consider that the antigen is completely destroyed following therapy or rather merely suppressed? What effect does cortisone have upon experimental pleuropneumonia infection, and does achromycin have the same in-vitro action as aureomycin against "L" organisms?

I wish to express appreciation to Dr. Brown for his very refreshing address. Those of the audience who wish to hear him in the near future are cordially invited to our Saturday Medical Clinic of December 18th.

One Merrymount Road
Baltimore 10, Maryland

HARRY F. KLINEFELTER, JR., M.D.† I feel extremely humble discussing this paper because I am really a neophyte in this field. My interest was stimulated in the Army, having never been stimulated before I served in the Army, and my experience is not in the research end at all but in the clinical application.

Before talking about the use that I have made of

* Professor of Medicine, University of Maryland.

† Chairman, Medical and Scientific Committee, Maryland Chapter of the Arthritis and Rheumatism Foundation.

the treatment he has discussed, I think it is important to emphasize that I am sure Dr. Brown didn't mean to imply that the patient should be treated only with small repeated doses of antibiotics, but that this treatment should supplement the general measures of treatment which we know are effective in bringing about a remission in a good many patients.

I have treated about sixty patients altogether, half in the clinic and half in my private practice. I have no statistics either, because I don't think statistics in this disease are fair unless one follows a patient four or five years or more, because of the factors which Dr. Wainwright and Dr. Brown both mentioned.

However, as a general thing, I have been impressed favorably with the results in private patients and unfavorably with the results in the ward or clinic patients. I have no ideas as to why that is, unless the clinic patients are in general at a lower nutritional level, or not intelligent enough to follow good general measures of treatment. Just what are the reasons, I don't know.

There are several things I would like to ask Dr. Brown. First of all, does he feel that cortisone, which is often necessary to keep these patients working, interfers in the long run with the over-all management directed at destroying this antigen with these small doses of antibiotics?

Secondly, I have not seen flare-ups occur, but I have not given large doses. However, I can recall one patient whom Dr. Futcher had on Osler 5, who was treated with large doses of terramycin and did not have a flare-up of her obvious rheumatoid arthritis.

Thirdly, I would like to ask Dr. Brown if he has attempted to culture these "L" organisms from the actual tissue of the synovial lining of the diseased joint. He mentioned that the fluid was sterile but I wonder if the organism can perhaps be cultured from the tissues of the joint on the egg embryo, or some other medium.

In contrast to Dr. Wainwright, although I know little about immunology and little about bacteriology, Dr. Brown's general theory has appealed to me. I have always been on the fringes of this theory, being a physician and clinician rather than a research man, but I certainly did enjoy hearing a further elaboration of his theory tonight, and want to express my personal appreciation to him for coming over and talking to us.

1101 North Calvert Street
Baltimore 2, Maryland

LEON A. KOCHMAN, M.D.* I am at a little bit of disadvantage by being the fourth discussant.

I enjoyed Dr. Brown's paper very much, and sometimes I feel like the cat on the fence. I don't know which way to jump; to believe, or not to believe, so convincing was the presentation.

Most of the discussion that can be offered has been very ably handled by both Dr. Wainwright and Dr. Woodward. Not being a microbiologist or an immunologist but rather more interested in the clinical aspects of rheumatoid arthritis, there are certain things I would like to ask Dr. Brown.

For instance, it is known that pleuropneumonia-like organisms can be recovered in the urethra of thirty per cent of normal people both male and female and that they can also be recovered from throat cultures in about seventy-five per cent of people who have had penicillin therapy, yet these people do not develop joint manifestations. I would like to know how he ties in his allergic or hypersensitivity idea on this basis.

Furthermore, if I heard the paper correctly, these organisms have been cultured. Why has no attempt been made to reproduce the condition in individuals by injecting pleuropneumonia-like organisms?

The third point mentioned concerned the advantages and disadvantages of the uses of cortisone. Yesterday at the American Rheumatism Association meeting in Washington, there was introduced a new compound, the chemical nature of which has not as yet been released. The treatment of seven patients with rheumatoid arthritis of varying degrees of progression, ranging in ages from sixteen to sixty-seven, with a disease duration from two-and-a-half to twenty-five years was given. These people had been treated by every known modality, including terramycin and cortisone in the methods which you have described, with no response whatsoever. Yet, with the use of this new preparation they have in three months time produced complete remissions with normal sedimentation rates which have been maintained; with an increase in albumin; with the

* Chief, Arthritis Clinic, University of Maryland.

reversal of the A/G ratio and with the marked improvement in the anemia picture with the restoration of the hemoglobin to normal. How do you tie that in to your picture of sensitivity?

And the one last question I should like to ask you. In spite of or, with all the work that you and your group have done in relation to the hypersensitivity idea in using terramycin with or without cortisone, do you have a regression or a stoppage of the pathological conditions in the joints, or is the disease still as progressive with your type of therapy as it is on the so-called standard modalities? Thank you.

3508 Denison Road
Baltimore 15, Maryland

GENERAL DISCUSSION

DR. BROWN: One question which was asked related to why the condition should not clear up immediately if the organisms were removed effectively by the antibiotic. We have indicated the probability that we are dealing with infection not as we have usually thought of it, but with hypersensitivity to an agent which is capable of both intra- and extracellular existence. If hypersensitivity were not present, then it would be theoretically possible to give large doses of the drug without flaring the disease, and immediate improvement, if not cure, would be expected. As L organisms have the properties of both bacteria and viruses, it is logical that the therapeutic approach might be considered a two-stage problem. The extra-cellular organisms could be reached easily, and this would account for the rapid clearing of positive cultures from prostatic secretions with small doses of the antibiotic. To reach the intracellular organisms would be more difficult and complicated by the hypersensitivity mechanism. Thus, to answer Dr. Wainwright's question concerning permanent remission, I can only say that on the basis of this concept it is possible. We may be seeing this now in some of our patients in whom this approach was started in 1949 and 1950. The final answer must await the analysis of a large series of long-term studies. Dr. Wainwright is concerned about difficulty of evaluation because of spontaneous remissions. He must of course be referring primarily to early cases where this is certainly true. In long standing cases who present the typical fluctuating but progressively downhill course over the years, and where the hematological aspects of activity have been persistent, we have seldom if ever seen a true sustained spontaneous remission with a return of the blood findings to normal. These are the patients we have been principally concerned with in the consideration of the effectiveness of therapy. There is another group of patients in whom lasting spontaneous remission can occur in nearly 80% of the cases. These are individuals who have reached the seventh decade in life. If rheumatoid arthritis represents primarily a form of deficiency to something, or an error in metabolism, or the result of stress, which possibilities represent the majority opinion at this time, would you not expect a worsening of symptoms rather than an improvement after seventy? According to our concept, there would be two possible explanations. One, that the parasite itself begins to die out because of the less favorable intracellular conditions at that age. The other would be that the reduced cellular activity would lower the rate of antibody formation, and decrease the antigen-antibody reactivity and thereby lessen symptoms.

Regarding the possible significance of L organisms from a pathogenic point of view, it is of interest that these organisms have been cultured twice as frequently from rheumatic subjects as from nonrheumatic subjects. Mrs. Robinson in our laboratory has cultivated L organisms from the joint fluid directly from only one arthritic, following many unsuccessful attempts. I think it should be reemphasized that the L organisms are extremely difficult to cultivate. Also, the stage of the disease may be important. Cultures for L organisms are more frequently positive early in the course of nonspecific urethritis. The toxic material liberated from the antigen-antibody reaction may inhibit growth as mentioned previously, and possibly many strains never achieve primary growth on artificial culture

media for this reason. We have encountered strains which have been seen only on initial culture and were not subculturable. Primary isolation in many cases may not be possible until better methods have been developed. The great difficulty has been that relatively little interest in this field has been manifest as yet, and much work remains to be done. Klieneberger-Nobel in London, Dienes and his co-workers, and our group are the only investigators to my knowledge who have persisted in the study of these organisms over these many years. We are now devoting a great deal of attention to studies of the metabolic requirements of these organisms, and I feel that until more is known about their growth requirements and identification in tissues the true incidence of their presence will be unknown.

It has been stated that the occurrence of these organisms in normal individuals minimizes their possible significance as human pathogens. Such an argument would not hold any more than the argument that meningococcus, the typhoid bacillus, the streptococcus, the pneumococcus, are not responsible for specific disease entities because they are found in normal individuals. The polio virus can be isolated from the stool of a great many normal carriers. We should also recall that the virus of atypical pneumonia—or so-called virus pneumonia—has not been definitely isolated or identified, and yet we do not hesitate to talk about this disease as caused by an infectious agent. Until human transmission of the hepatitis virus was observed, that condition was considered to be due to a toxic substance or some catarrhal influence. Dr. Wainwright also opposes these views because we cannot reproduce this disease in animals. It has been pointed out that L organisms are highly species specific. It is unfortunate that strains which produce arthritis in one species will not affect another species in a similar manner. But it is a very important fact that the L organisms as a group have a greater affinity for joints than any other agents known in the entire microbiological realm. There are a number of infectious diseases of man that cannot be reproduced in animals, such as typhoid fever, scarlet fever, meningococcal meningitis, the common cold, infectious hepatitis, etc.

I was very glad to hear that Dr. Klinefelter had noticed an effect in some of his patients. I don't know why his clinic patients fail to do as well as his private patients. I presume that one of the reasons is that the clinic patients do not live under ideal conditions, and consequently their disease is more apt to flare during treatment. I think that if he continues to treat them long enough, however, the end result will be the same in both groups. In regard to this treatment, it is important to remember that it may take a very long time for remission to be established. Once it has been fully established, our patients have held their improvement very well. They may require short courses of low-dosage antibiotic therapy if they show signs of any return of the trouble. But this is very effective when a point is reached where the blood findings are apparently normal. I might say that there is one particular group of patients who fail to continue to improve on the low-dosage method later on in treatment. When a plateau of improvement has been reached, we have employed larger doses, such as 250 mgms. of achromycin or aureomycin three times daily for three days in repeated courses every other week. Many of the aspects of these particular cases remind one of chronic brucellosis. These are the individuals who usually present the most marked psychological abnormalities. Mental depression is common, and it comes in cycles as we often see in chronic brucellosis. They may have night sweats, which is common in chronic brucellosis, and many have had unexplained fever in the past. They usually appear very much more alert than the other rheumatoid arthritics, and anemia is uncommon even with considerable joint abnormality. The Kunkel globulin may be slightly elevated, as may be the total globulin, and the sedimentation rate is usually not high. After many months of low-dosage therapy and at a time when increased dosage can be well tolerated, the intermittent courses of larger doses may produce a marked further improvement. I might add that these patients almost uniformly give a history of raw milk consumption in the past and may have had leg and muscle cramps and aches, as well as periodic episodes of fatigue for which there has been no explanation. Brucella agglutinations, even with the Coombs modification, usually have not revealed positive tests. Occasionally diagnostic agglutination titers for Brucella have been obtained. Some in this series have had a positive previous diagnosis of Brucellosis and behaved in a manner identical to those in whom the diagnosis cannot be established.

We can only speculate that they may fall into the group where the primary infection was by the Brucella organism, and we hope that a better method of diagnosis can be developed in the future.

In answer to Dr. Klinefelter's question about the attempt to culture L organisms from the tissues of the synovium, I can only say that we have tried this in the past and have been unsuccessful. In recent years we have made every attempt to avoid animal inoculation because of the objection to the possibility of recovering an agent from the experimental animal. We feel that tissue culture techniques may have to be employed because of the difficulty of growing L organisms on artificial media. Again, if we can receive the proper support and interest in this field to develop adequate facilites, we would very much like to work on this particular phase of the problem. Dr. John Adams has been performing synovial biopsies for us for pathological study only thus far.

In reference to another of Dr. Klinefelter's questions, we most certainly do treat the patient as a whole at all times. We give salicylates, vitamins, iron and physiotherapy and high protein diets as we see fit. None of these methods of management interferes with evaluation of results because our patients have used these methods extensively in the past without sustained improvement. We seem to collect patients who have failed to maintain improvement by any other method. The most difficult problems have been a considerable number of patients who have had late progressive worsening on cortisone therapy. We have attempted to control the factor of psychological influence the physician may have on the disease by seeing patients infrequently. Many of our patients are seen no more often than every four months. The safe aspects of these antibiotics compared to gold salts or cortisone makes this possible. It is also of interest that the emergence of bacterial resistance of intestinal bacteria has not been observed with these low dosages, even after several years of treatment. In preliminary studies, Mrs. Robinson has not encountered L strains which have revealed the development of resistance. This appears to be a unique property of these organisms and would correlate well with their probable intracellular existence where their metabolic needs might be more easily met. This is unlike other bacteria, which possess the chemical ability to manufacture substances for food and defense.

Dr. Kochman has referred to cortisone and has mentioned his great interest in the new compounds which are being investigated at the National Institutes of Health. I personally would predict that the more potent the steroid, the greater the ultimate danger to the patient because of the effect on the immune mechanism. The increased articular destruction noted on X-ray in cortisone-treated cases, which appears more rapid in some individuals, at least, than in untreated patients, would possibly be an example of interference with the immune mechanism by cortisone. In my opinion, there has been far too little attention to the underlying mechanisms of this disease, and too much attention to drugs. We have listed a number of anti-L substances, none of which is ideal as yet because of their low intracellular concentration. We now know the direction we should follow. You will note that basic studies on bacterial variation in general and the L organism in particular may be the essential navigation instruments necessary to keep us on the right course.

I would particularly like to thank Dr. Woodward for his remarks. He has seen the most important point of all, namely that through this work we have begun to realize that the host response is as important in disease as the parasite itself. This understanding may of course allow us to broaden our thinking to include many other fields such as hypertension, multiple sclerosis, vascular diseases and possibly neoplastic diseases.

May I thank you again for the evening here and for your interest.

Component Medical Societies

ALLEGANY-GARRETT COUNTY MEDICAL SOCIETY

LESLIE E. DAUGHERTY, M.D.
Journal Representative

Cumberland Heart Association

At the meeting of the Allegany-Garrett County Medical Society of November 18, a discussion of the "Heart Association" was brought up and our stand of the December meeting, at which Dr. Love spoke, was reaffirmed. At that time, the Society went on record as "approving the principle of the Maryland Heart Association."

Seventeen members of the Society are on the advisory board of the Allegany-Garrett County Heart Association and have held several meetings during the year. The previous Heart Clinic was not under the Heart Association, but was run by the State Health Department.

The medical advisory committee to the local Heart Association devised a method of caring for the medically indigent cardiac cases through the local Heart Association. Any patient in need of such service, will be referred through that office by his family physician for consultation, evaluation, or rehabilitation. The patient on doctors recommendation will also be given oral penicillin as long as necessary, free of charge.

The consultants will be volunteers from our own Society, who are interested in cardiac diseases. These physician's names will be on the roster at the Heart Office and the referring physician will have his choice (or if no choice, the next name down the list.) The consultants will submit a full written report to the referring physician. If further consultations (or treatment) are necessary the case will be referred to the Heart Association in Baltimore. These facilities are under the supervision of Drs. Love and Taussig.

Civic Group Seeks Physician in Mt. Savage

Mt. Savage, Allegany County, is temporarily without its only physician, Dr. William E. Moseley, who has been unable to practice since August, 1955, and Mt. Savage Civic Groups conferred with the Allegany-Garrett County Medical Society, requesting that a physician be located there.

A new industry has located in Mt. Savage, which recalls the memory of a once thriving manufacturing town. Dr. Arthur H. Hawkins, deceased, a former president of the Medical and Chirurgical Faculty, began his practice in Mt. Savage. Since then Dr. F. Garnett Cowherd, deceased, Drs. F. A. G. Murray, Samuel E. Enfield and J. Kyle Cowherd and H. J. Bostetter, were located there.

Miners Hospital Opens New Addition

The new maternity wing at Miners Hospital, in Frostburg, Maryland opened on December 4. Credited for sponsoring plans and completion of the new addition was Dr. John C. Devers, chairman of Health and Welfare, of Frostburg Civic Club group. The maternity ward equipment was donated by the Club.

Civil Defense

Organization for Medical Care has been completed in Allegany County, and practice drills are now being held throughout the County.

Casualty Clearing Stations, #1 and #2, with Drs. G. Overton Himmelwright and Clay E. Durrett, as Medical Chiefs, have organized a disaster (training) corps and are serving as instructors in the training of First-Aid Station personnel, under the supervision of Dr. Leo H. Ley, Jr., of Cumberland, who is Deputy Director for Administration, in Allegany County.

Personals

Dr. Arthur F. Jones, Health Officer of Garrett County, is featured in Cumberland's local newspaper, of "Happenings of Thirty Years Ago." He was a guard on the football team, known as the "Biting Bulldogs" of 1925.

Dr. Hilda J. Walters, Frostburg, Maryland spoke at a recent meeting of the Beall Elementary School

Parent Teacher's Association. Her subject was "Prevention of Heart Disease in Children."

Dr. Leslie Miles, of Huntington, West Virginia and lately of Capon Bridge, West Virginia is now located at 27 Main St. Lonaconing, Maryland doing General Practice. Dr. Miles graduated from the University of Maryland and did his premedical work at West Virginia University.

BALTIMORE COUNTY MEDICAL ASSOCIATION

WILLIAM A. PILLSBURY, M.D.

Journal Representative

We are sorry to record the recent death of Dr. Walter M. Carmine of Dundalk, a beloved member of our association.

The November meeting was held at the St. Agnes Hospital on November 16. This was the first time that the Baltimore County Medical Association has held a meeting at this hospital. After introductory remarks by Dr. James G. Howell, Dr. Carl F. Mech, the guest speaker, gave an informative and challenging talk on "Why Gastrointestinal Surgery?"

The following members were nominated to be the next year officers:

President—Dr. Louis Z. Dalmau, Pikesville

Vice President—Dr. William A. Pillsbury, Timonium

Secretary-Treasurer—Dr. Charles Lee Randol, Pikesville

Delegates—Dr. Melvin B. Davis, Dundalk; Dr. Charles F. O'Donnell, Towson; Dr. Martin E. Strobel, Reisterstown

Alternates—Dr. David H. Andrew, Dundalk; Dr. Charles H. Williams, Pikesville; Dr. Paul H. Royse, Pikesville

CECIL COUNTY MEDICAL SOCIETY

MILFORD H. SPRECHER, M.D.

Journal Representative

Dr. James Magraw of Perryville, Maryland has recently been designated an emeritus member of the Society. He has been one of the most active members of The Cecil County Medical Society, having served at various times in all of the elected offices of the Society. He is a community figure, having helped to organize the Community Fire Company of Perryville, and has been its director for many years. He was one of the organizers of the National Bank of Perryville and has served as director and president for about twenty years. Twice he was appointed to the Board of Directors of the Eastern Shore State Hospital and served until his health would not permit him to continue. When the Jacob Tome Institute was operating at Port Deposit, Maryland he was on the Board of Directors.

Dr. Magraw attended and graduated from the Havre de Grace High School in 1905 and was graduated from the University of Maryland School of Medicine in 1909. After an internship at the University Hospital he went to Rocky Mount, N. C. with the Atlantic Coast Line Railroad, which he served for about three years. Following that he returned to Perryville and went into partnership with his uncle, Dr. George M. Stump. He has served continuously until 1951 a general practice involving Cecil County and much of Harford County.

DORCHESTER COUNTY MEDICAL SOCIETY

ALFRED R. MARYANOV, M.D.

Journal Representative

The regular December meeting of the Dorchester County Medical Society was held at the Cambridge Country Club, on December 7, 1955. The wives of the members were present for dinner as guests of the Society.

The meeting was called to order by the president, Dr. Wolff.

Those present were Drs. Baumann, Bunker, Burdette, Hanks, Hastings, Jr., Hastings, Sr., Johnson, Kenneth Jones, Mace, A. Maryanov, L. Maryanov, F. Miller, R. Miller, Reddick, Thompson, Traub, West, Jr., West, Sr., E. Winiarz, W. V. Winiarz, and E. H. Wolff.

Election of Officers:

President—Dr. George Currier. Nominated by Dr. A. Maryanov and seconded by Dr. L. Maryanov. Nominations closed. Secretary cast a unanimous ballot in favor of Dr. Currier.

Vice-President—Dr. Wilbur Baumann. Nominated by Dr. Reddick and seconded by Dr. F. Miller. Nominations closed. Secretary cast a unanimous ballot in favor of Dr. Baumann.

Secretary-Treasurer—Dr. L. Maryanov. Nominated

by Dr. F. Miller and seconded by Dr. Mace. Nominations closed. Secretary cast a unanimous ballot in favor of Dr. L. Maryanov.

Delegate—Dr. F. Miller. Nominated by Dr. Mace and seconded by Dr. Burdette. Nominations closed. Secretary cast a unanimous ballot in favor of Dr. Miller.

Alternate Delegate—Dr. William Hanks. Nominated by Dr. F. Miller and seconded by Dr. Burdette. Nominations closed. Secretary cast a unanimous ballot in favor of Dr. Hanks.

Meeting adjourned at 7:45 p.m.

FREDERICK COUNTY MEDICAL SOCIETY

LOUIS R. SCHOOLMAN, M.D.

Journal Representative

The regular November meeting was held at the Frederick Hotel on the 15th. Elections in the society are held in the same month as those of local and national importance. The traditional buffet supper "on the treasury" was served. Mine host, genial Mike Croghan, presided over the trays of oysters on the shell, fried oysters, country ham, baked beans, celery and olives, sharp cheddar cheese and crackers and dark rye bread, beer and coffee. All ad lib. Your correspondent freely admits that only on this occasion does he ever get as many oysters as he really wants.

The elected officers were:

President—Norvell Belt
First Vice President—James B. Thomas
Second Vice President—Jesse Fifer
Secretary—A. M. Powell
Treasurer—John Culler
Censor—Thomas Quill
Delegate—L. R. Schoolman
Alternate—Henry Chase

An instructive movie on nephrosis of childhood was shown through the courtesy of the Pfizer Company.

Hospital Events

At the regular November meeting of the medical staff three interesting case reports were presented. They were: "Foreign Body in the Oesophagus Causing Excruciating Chest Pain" by Dr. Chase; Fibroelastosis of the Heart Causing Sudden Death in a Seven Weeks Old Infant by Dr. Turner; and A Case of Stokes Adams Syndrome with as Many as Twenty-six Attacks in One Day by Dr. Stone.

The medical department had two meetings. At the first Dr. Thomas Stone spoke on virus pneumonia and at the second Dr. Rex Martin spoke on complications of diabetes.

The pediatric department decided to engage in a joint monthly postgraduate program with the medical department.

The case at the November C.P.C. was that of a large subdural hematoma which had eluded the diagnostic efforts of the neurosurgery department of a large medical college. It also eluded ours. But it was a good object lesson.

MONTGOMERY COUNTY MEDICAL SOCIETY

MAYNARD I. COHEN, M.D.

Journal Representative

Tuesday, December 20, 1955, the Montgomery County Medical Society met at the Norbeck Country Club, Norbeck, Maryland. Speaker for the evening was Dr. John C. Krantz, of the School of Pharmacology, University of Maryland, in Baltimore. His talk on "The Pharmacology of Alcohol" was very well received.

The Society extended a vote of thanks to Dr. James McCarrick and the Dance Committee of the Ladies Auxiliary for a most successful annual dinner dance at the Woodmont Country Club in November.

The parking lot in the rear of the Faculty Building is open every day until five o'clock for your convenience. Enter from Maryland Avenue. You'll find it particularly useful when you need a stack of books or journals from the library.

Necrology

A. S. CHALFANT, M.D., *Chairman*

Memoir Committee

Walter M. Carmine, M.D.

1881–1955

Dr. Walter M. Carmine passed away suddenly and quietly in his sleep at the age of 74.

Born in Preston, Maryland, he received his B.A. degree from Washington College at Chestertown in 1903 and his M.D. from the University of Maryland in Baltimore in 1907, returning to Chestertown to earn his master of arts degree in 1908. After a period as physician for the Bethlehem Steel Shipyard, in Sparrows Point, he practiced continuously in Dundalk.

Dr. Carmine's service to the people of Dundalk was augmented by work on many other health boards and associations. Among these tasks was that of deputy county medical examiner for more than two decades, a post he filled up to the time of his death, county registrar, detached service as medical examiner of the Maryland National Guard for the past eight years; the Volunteer Medical Corps during World War I and as examining physician of the Dundalk Selective Service Board during World War II; examining physician of the Army Main Induction and Recruiting Station in Baltimore for a decade, and a member of the Baltimore County Health Association Board.

In addition, he made countless examinations of school children working for the County Health Department. He is a past president of the Baltimore County Medical Association. He also was a member of the following organizations: the Medical and Chirurgical Faculty of Maryland, John H. Latrobe Lodge No. 165, AF & AM; Concordia Council No. 1, R&SM: St. John's R.A. Chapter No. 11 and he was a former Rotarian. He was one of the first members of the Sparrows Point Country Club and continued as a member until his death.

Surviving the doctor are his wife and daughters, Miss Eugenia Carmine and Mrs. J. Alden Kappel and grand-daughter, Judith A. Kappel, all of Dundalk.

Dr. Walter Carmine has passed on to his reward, and the people who were his patients, those who worked with him and those he worked for will long remember the man who devoted his life to alleviating the pain and suffering of others.

Victor D. Miller, M.D.

1875–1955

Dr. "Vic" as he was known to medical and business associates as well as to his many patients, started practicing medicine in Hagerstown in 1901. He graduated from Mercersburg Academy, Princeton University and the Medical School of the University of Pennsylvania and had served a year on the staff of the German Hospital in Philadelphia and six months in King's Hospital, Brooklyn, New York before entering into active private practice.

He was one of the four Doctor Millers who were engaged in the practice of medicine here at one time. The father, Dr. Victor D., Sr., educated his three sons, Victor, DeWitt Clinton and William Preston—as medical doctors and all became prominent in their profession and in the civic affairs of Hagerstown and Washington County.

Dr. Vic, the last of the quartet, started practice with his brother, Dr. William Preston Miller and his career was uninterrupted until his recent illness. Needless to say, his patients down through the years numbered in the thousands.

Always a close student of medicine, Dr. Vic maintained a leading role in General Practice up until his death.

He became a member of the Medical Staff of the Washington County Hospital when it was organized in 1905 and was a staunch supporter of the institution henceforth. He was long a member of the American Medical Association, the Washington County Medical Association, the Cumberland

Valley Medical Association, and the Medical and Chirurgical Faculty of the State of Maryland.

He was past president of the Hospital Staff and served as a member of the First Board of the YMCA. He also served as president of the Washington County Chapter of the Red Cross, the County Public Health Association, the Hagerstown Chamber of Commerce, the Hagerstown Rotary Club, Fountain Head Country Club and the Hagerstown Auto Club. He served on the Medical Advisory Committee of the local Draft Boards during World Wars I and II. He was a devout member of Zion Evangelical and Reformed Church, Hagerstown.

Surviving him are his wife, Nellie B. Loose Miller; daughter, Mrs. Helen Miller Mathias, Hagerstown, and sons, Victor D., Hagerstown, and Colonel Henry L. Miller, Fort Myer, Virginia; sisters, Mrs. Henry Spangler, Mercersburg, Mrs. Calvin Gabriel and Miss Mary Miller, both of Baltimore. Four grandchildren survive.

Excerpted from the Hagerstown Herald Mail.

W. Hamilton Smith, Jr., M.D.

1883–1955

Dr. W. Hamilton Smith, Jr., local ear, nose and throat specialist, died Monday, November 7, 1955 at Washington County Hospital. He was aged 72 and the last surviving member of his family.

A native of Washington, D. C., he was a graduate of George Washington University and served in the U. S. Army Medical Corps as a surgeon in World War I. He was discharged with the rank of major.

A practicing physician and surgeon in Washington County for many years, he was past president of the County Medical Society. He was also a member of the American Medical Association, the Medical and Chirurgical Faculty of Maryland and was a fellow in the American College of Surgeons.

Dr. Smith was a member of Trinity Lutheran Church, and of the Sunday School orchestra. He was also a member of Masonic Lodge No. 217, Hagerstown.

Surviving him are his son, W. Hamilton Smith, III and two grandchildren.

George A. Stewart, M.D.

1885–1955

After a brief illness of three days, Dr. George A. Stewart died at The Johns Hopkins Hospital on April 23, 1955.

Just four weeks earlier he had been given a testimonial dinner by twenty-four former residents of St. Agnes Hospital. These doctors had been at the hospital between 1933 and 1954, at which time Dr. Stewart became Surgeon Emeritus. "The earlier ones in this group lived and worked with him as a tart and exacting teacher; those of a later day have known him as a more mellow but still exacting surgeon." Thus wrote the young surgeons who had completed surgical residences under his guidance.

Dr. Stewart was born in Philadelphia on February 28, 1885, the youngest child of John McEntire Stewart and Mary Catherine Bond Stewart. He lived the greater part of his life, however, in Baltimore where he graduated from Baltimore City College in 1904. He graduated from The Johns Hopkins University in 1907 and from The Johns Hopkins Medical School in 1911.

Following his graduation in medicine, Dr. Stewart entered St. Agnes Hospital as interne where he was closely associated with one of his former teachers, world renowned surgeon and cancer specialist, Dr. Joseph Colt Bloodgood. This association continued until Dr. Bloodgood's death in 1935.

Following his residency at St. Agnes Hospital, Dr. Stewart enlisted in World War I as a lieutenant in the Medical Reserve Corps. A few weeks later he was made Surgeon-in-Charge and Commanding Officer, U. S. Army Auxiliary Hospital No. I, War Demonstration Hospital Rockefeller Institute of Medical Research. Here he collaborated in the treatment of infected wounds by the Carrel-Dakin method. For this he was decorated by the French government for War Service "Ministere del'Interieur, Assistance Publique."

In World War II Dr. Stewart served in the Army of the United States as Lieutenant Colonel at Fort Belvoir, Virginia, from March, 1941 to November 1942, and as Colonel at Oliver General Hospital, Augusta, Georgia, in both places being Chief of the Surgical Service.

In September, 1945 he was transferred to Atlanta, Georgia to become Surgical Consultant and Chief of Professional Service Branch, U. S. Army Headquarters Fourth Service Command. Upon his retirement from active military duty in April, 1946, Dr. Stewart became Civilian Consultant in Surgery, and in this capacity made an inspection tour of the Army hospitals in Germany.

In addition to his work at St. Agnes Hospital, Dr.

Stewart was Chief Surgeon at Bon Secours Hospital, Associate in Surgery at The Johns Hopkins School of Medicine, Assistant Professor of Surgery at The Johns Hopkins School of Medicine, and Surgeon in the Tumor Clinic in the OPD, The Johns Hopkins Hospital. On July 1, 1950 he was made Assistant Professor Emeritus of Surgery, The Johns Hopkins School of Medicine.

His publications included "Intestinal Obstruction due to Meckel's Diverticulum," "Treatment of Empyema by the Carrel-Dakin Method at the War Demonstration Hospital," "Carrel-Dakin Treatment of Infected Wounds," "A Present Day Approach to the Problem of Cancer," and "Tumor of the Chest Wall." With Dr. Joseph Colt Bloodgood he wrote a paper on "Preoperative Irradiation of Breast Tumors" and collaborated with Dr. L. Clarence Cohn on the subject of "Tumors of the Lateral Thyroid Component."

He was greatly interested in the Y.M.C.A., both at Levering Hall, J.H.U., and the Central Branch, and in the Bolton Street Center of the Brown Memorial Presbyterian Church, of which he was an Elder. From the early days of the P.A.L., Dr. Stewart was active in athletic meets and was a member of the Officials Club.

On January 8, 1921, Dr. Stewart married Dr. Eleanor B. Wolf, a graduate of Goucher College and of The Johns Hopkins Medical School. Prior to her marriage Mrs. Stewart served for six years as a medical missionary in India. Dr. and Mrs. Stewart have one son and three grandsons.

Dr. Stewart belonged to many professional societies, having been for many years Chairman of the Committee on Scientific Work and Arrangements of the Maryland Medical and Chirurgical Faculty. He was a member of the Founders Group of the American Board of Thoracic Surgeons, the Founders Group of the American Board of Surgery, Past President of the American Association for the Study of Neoplastic Diseases, and a Fellow of the American College of Surgeons.

Dr. Stewart led a busy life, an interesting life, a worthwhile life. His church and his home were near his heart. He was a friend to worthy students, vitally interested in athletics, a perfect host in his home. Dr. Stewart will be genuinely missed in the City, in the many organizations of which he was a member and in his wide circle of friends. He will be long remembered, respected, and admired by this community.

E. Van Teagarden, M.D.

1896–1955

Dr. E. Van Teagarden died unexpectedly at his home on September 5, 1955. He was born on June 4, 1896, in Endicott, West Virginia, the son of the late Dr. and Mrs. William Van Teagarden. He is survived by his wife, the former Bertha Cecelia Rosiak; three daughters, Mrs. John G. Gregory of Baltimore, Maryland, Mrs. John J. McLaren of Boston, Massachusetts, Mrs. George L. Pasquella of Greenbelt, Maryland; a son, Arthur, who is a pre-medical student at the University of Maryland; a sister, Mrs. Maurice R. Dodd of Lakeland, Florida and a grandson, Dan Stephen Pasquella.

Dr. Teagarden was a veteran of World War I and saw service in France while in the Army with the 64th Regiment, American Expeditionary Forces. After his discharge from the Army, he continued his education and received his B.S. degree from West Virginia University in 1924 and his M.D. degree from the University of Maryland in 1926. He interned at the Baltimore City Hospitals and the University of Maryland Hospital and served as resident at Sydenham Hospital. Dr. Teagarden specialized in Industrial Medicine and was Assistant to the Chief Physician of the Baltimore Gas and Electric Company from 1927 to the time of his death.

Dr. Teagarden was a member of the Medical and Chirurgical Faculty of Maryland, Baltimore City Medical Society and the Maryland Academy of Medicine and Surgery of which he was President in 1952–1953.

Dr. Teagarden was a man of high principles, a conscientious physician and a loyal friend to his patients. He was an ardent reader and kept informed on new developments in medical research and practice. His passing is a great loss to his profession, his family and his friends and associates. As one of his beloved patients has so aptly memorialized him: "Our own hearts go on a little better, a little kinder and a little more educated for having known the splendid great heart of 'Doctor Van'."

Library

"Books shall be thy companions; bookcases and shelves, thy pleasure-nooks and gardens." *ibn Tibbon*

TYPHOID FEVER

LOUIS KRAUSE, M.D.*

The story of typhoid fever goes back many years into the early history of mankind. While we do not have evidence that is conclusive, certainly the references can be interpreted to support such a possibility. It is tantalizing and tempting to read Proverb 5:15 which is as follows: "Drink waters out of thine own cistern, and running waters out of thine own wells," to support the possibility that observations were already made at that time of the hazard of drinking water except from one's own well. While this reference is used for moral purposes, it is interesting to speculate on the origin of such an observation.

We can be more certain of typhoid when we read the notes of the attendant of Alexander the Great. I think these notes leave a medical man in no doubt as to the disease which killed Alexander the Great. It was certainly typhoid and not alcohol as is frequently stated. The frequency with which this occurred can be only surmised from other literary records. From literary remains in the medieval period we begin to get a little more support.

In the 1600's we have records that indicate the recognition of some of the pathology of typhoid particularly in the time of Thomas Willis, the clinician. There was still no clear cut separation made between typhoid and typhus fever. Clinically it was still confused with typhus and was known as nervous fever (the so called nerber fieber of the Germans). The clinicians referred to typhoid with spots as typhus and typhoid fever as abdominal typhus.

In the early 1800's in France, we certainly have clinical identification of typhoid described by Pierre Bretonneau. He described the enlarged Peyer patch as a button and he called it with a Greek name signifying a button i.e. Dothien enteritis. He had an American with him for a year or more named William Wood Gerhard from Philadelphia. When Dr. Gerhard returned to his home, he observed the same clinical picture in Philadelphia, and he emphasized the difference between typhoid and typhus fever in a publication in 1837. To be sure, not all the details were noticed. For instance, the familiar rose spot of typhoid escaped attention.

In 1800 the organism responsible for typhoid fever was identified and recognized by Carl Joseph Eberth of Germany. No effective treatment or prevention was available until the beginning of this century. A preventative was developed proving to be effective and for the first time great outbreaks of typhoid did not occur. In World War One disease did not kill more men than bullets did in the American Army.

A therapeutic agent, chloramycetin was developed in the last decade. This remedy developed from a fungus found in the soil of Venezuela. Today, with the enforcement of the old adage of "3 f's," fingers, flies, and food as being responsible for the transmission of typhoid. We have little typhoid fever and the therapeutic agents did well to keep the disease under control.

You will find many interesting references to the history of this devastating illness in the following books:

Currie, J. Medical reports on the effects of water, cold and warm, as a remedy in fever and other diseases. 2d.ed. London, Cadell & Davies, v.1, 1798, v.2, 1805.

Petit, M. A. Traité de la fievre entéro-mésenterique, observée, reconnue et signalée publiquement à l'Hotel-Dieu de Paris, dans les annees 1811, 1812 et 1813. Paris, Hacquart, 1813.

Smith, N. A practical essay on typhous fever. N. Y., E. Bliss & E. White, 1824.

* Chairman, Library Committee.

Louis, P. C. A. Anatomical, pathological and therapeutical researches upon the disease known under the name of gastro-enterite, putrid, adynamic, ataxic or typhoid fever, etc. Boston, Isaac R. Butts, 1836.

Jackson, J. A report founded on the cases of typhoid fever, or the common continued fever of New England, which occurred in the Massachusetts General Hospital, from the opening of that institution, in September, 1821, to the end of 1835. Boston, Whipple & Damrell, 1838.

Hale, E. Observations on the typhoid fever of New England. Boston, Whipple & Damrell, 1839.

Stewart, A. P. Some considerations on the nature and pathology of typhus and typhoid fever, applied to the solution of the question of the identity or non-identity of the two diseases. *In* Selected monographs. London, New Sydenham society, 1884. (Publications, v. 110)

Forget, C. P. Traite de l'enterite folliculeuse (fièvre typhoïd). Paris, J. B. Baillière, 1841.

Bartlett, E. The history, diagnosis, and treatment of typhoid and of typhus fever. Phila., Lea & Blanchard, 1842.

Flint, A. A memoir on the transportation and diffusion by contagion, of typhoid fever. Supplement to "Clinical reports on continued fever." Buffalo, G. H. Derby, 1852.

Wunderlich, K. R. A. On the temperature in diseases: a manual of medical thermometry. London, New Sydenham society, 1871. (Publications, v. 49.)

Budd, W. Typhoid fever: its nature, mode of spreading, and prevention. London, Longmans, Green, 1873.

Maryland State Board of Health. Special report on the prevalence of typhoid or entero-miasmatic fever at Cumberland, Md. By C. W. Chancellor. Balto., W. K. Boyle, 1891.

Sihler, C. The hydriatic treatment of typhoid fever, according to Brand, Tripier and Bouveret, and Vogl. Cleveland, C. Sihler, 1891.

Keen, W. W. The surgical complications and sequels of typhoid fever. Phila., W. B. Saunders, 1898.

Hare, H. A. The medical complications, accidents and sequelæ of typhoid or enteric fever. Phila., Lea Bros., 1899.

Corfield, W. H. The etiology of typhoid fever and its prevention. London, H. K. Lewis, 1902. (Milroy lectures)

Nichols, J. B. Diet in typhoid fever. Providence, Snow & Farnham, 1907. (Fiske fund prize dissertation, no. 50)

Naegeli, O. Blutkrankheiten und Blutdiagnostik. Leipzig, Veit, 1908.

Whipple, G. C. Typhoid fever; its causation, transmission and prevention. N. Y., J. Wiley, 1908.

Lumsden, L. L. The causation and prevention of typhoid fever. Wash., U.S. Gov't. print. off., 1912. (Public health bulletin no. 51)

Gay, F. P. Typhoid fever considered as a problem of scientific medicine. N. Y., Macmillan, 1918.

Webb-Johnson, A. E. Surgical aspects of typhoid and paratyphoid fevers, founded on the Hunterian lecture for 1917. London, H. Frowde, Oxford Univ. pr., 1919.

Garbat, A. L. Typhoid carriers and typhoid immunity. N. Y., Rockefeller institute for medical research, 1922. (Monograph no. 16)

Hume, E. E. Max von Pettenkofer, his theory of the etiology of cholera, typhoid fever and other intestinal diseases, a review of his arguments and evidence. N. Y., P. B. Hoeber, 1927.

Browning, C. H., and others. Chronic enteric carriers and their treatment. London, H. M. Stat. off., 1933. (Medical research council special report series no. 179).

Havens, L. C. The bacteriology of typhoid, Salmonella, and dysentery infections and carrier states. N. Y., Commonwealth fund, 1935.

U.S. Army medical school, Washington, D. C. Immunization to typhoid fever; results obtained in the prevention of typhoid fever in the United States army, United States navy, and Civilian conservation corps, by the use of vaccines. Balto., Johns Hopkins pr., 1941.

Many original contributions on the subject are to be found in journals which the library staff will be happy to supply to interested readers.

The library now receives 325 journals regularly. From "Acta" to "Zeitschrift," the best of the current medical literature is available for your use in our comfortable reading room. If you like, the library staff will be happy to set aside material on a specific subject for you.

Health Departments

BALTIMORE CITY HEALTH DEPARTMENT

The City's Official Population Figure

Each year the City Health Department prepares estimates of the City population in order to determine the magnitude of various health problems. These estimates are based upon a study of previous population trends, knowledge of the number of births and deaths among residents of the city and an estimate of the migration of the population. The Director of the Statistical Section, Dr. Matthew Tayback, has completed his estimate of the city's population as of July 1, 1955 and finds that the population at that time was 966,000 which is the same population estimated for the previous year as of July 1, 1954.

White-Negro Proportion Changes

Although there was no change in the size of the total population, the white segment is estimated to have declined from 708,000 in 1954 to 700,500 in 1955, a loss of 7,500 persons. The nonwhite population increased from 258,000 to 265,500 a gain of 7,500 persons.

It is of some interest to examine the manner in which these population changes have taken place during the year, July 1, 1954–July 1, 1955. The natural increase among white residents, that is, the excess of births over deaths was 7,200. However, there was a net out-migration of white residents amounting to 14,700. This out-migration combined with the natural increase resulted in a decline of 7,500 white residents. In the colored population the natural increase was 6,100 and the net in-migration was 1,400 giving an increase of 7,500 in the colored segment.

A number of questions arise as a result of this type of population trend which has been apparent for the past several years. One may ask, how is it with a large scale program of residential construction in the peripheral areas of the city that the total population does not show an increase? The explanation advanced by Dr. Tayback is that a considerable decline is taking place in the population of the innermost parts of the city due to demolition and the not inconsiderable conversion of residential housing to commercial usage. A second question which arises is whether the City of Baltimore is unique in the pattern of in-migration of colored persons and a net out-migration of white persons. This is not a pattern which is unusual in the major cities of this country. Our neighbor to the south, Washington, D. C. and such cities as Philadelphia, New York City, Chicago and Detroit all have experienced in recent years, a significant rise in the colored proportion of the total city population.

The third question which is of especial interest to health and social authorities is concerned with the influence which recent demographic trends in the major cities have on health and welfare programs. From a health point of view these recent trends are significant because they result in an aging of the white population remaining in the major cities since it is the younger element that does most of the moving. Contrariwise, the colored community in the city continues to remain a relatively young population because its growth results from a high birth rate and from the additions of young adults by in-migration.

It may be somewhat disappointing to many who read of these recent demographic trends to note that the population in this great metropolis is not increasing in a significant way. It should be understood that the available land area for residential usage is limited and some day may be completely occupied. This limit, of course, has not been reached in Baltimore and with a vigorous urban renewal program there is good reason to believe that the eventual population for the City of Baltimore may be in the neighborhood of 1,200,000.

Huntington Williams, M.D.

Commissioner of Health

STATE OF MARYLAND DEPARTMENT OF HEALTH

MONTHLY COMMUNICABLE DISEASE REPORT

Case Reports Received during 4-week Period, January 1–26, 1956

	CHICKENPOX	DIPHTHERIA	GERMAN MEASLES	HEPATITIS, INFECT.	MEASLES	MENINGITIS, MENINGOCOCCUS	MUMPS	POLIOMYELITIS, PARALYTIC	POLIOMYELITIS, NON-PARALYTIC	ROCKY MT. SPOTTED FEVER	STREP. SORE THROAT INCL. SCARLET FEVER	TYPHOID FEVER	UNDULANT FEVER	WHOOPING COUGH	TUBERCULOSIS, RESPIRATORY	SYPHILIS, PRIMARY AND SECONDARY	GONORRHEA	OTHER DISEASES	DEATHS: Influenza and pneumonia
Total, 4 weeks																			
Local areas																			
Baltimore County	43	—	10	2	154	—	44	—	—	—	7	—	—	1	20	—	1	—	9
Anne Arundel	12	—	1	—	17	—	12	—	—	—	2	—	—	1	10	—	1	—	6
Howard	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1
Harford	1	—	3	—	3	—	—	—	—	—	4	—	—	—	1	1	—	—	—
Carroll	—	—	—	1	—	—	1	—	—	—	—	—	—	—	—	—	2	—	2
Frederick	18	—	1	2	32	—	—	—	—	—	7	—	—	2	3	—	3	—	2
Washington	10	—	—	—	54	—	4	—	—	—	—	—	—	—	10	1	3	—	2
Allegany	1	—	—	2	17	—	—	—	—	—	3	—	—	—	1	—	—	—	2
Garrett	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Montgomery	39	—	—	1	21	1	7	1	—	—	10	—	—	—	14	—	5	—	14
Prince George's	5	—	—	—	4	—	3	—	—	—	3	—	—	—	8	—	1	—	7
Calvert	2	—	—	—	—	—	4	—	—	—	—	—	—	—	1	—	1	—	—
Charles	2	—	—	—	—	—	1	—	—	—	1	—	—	—	—	—	—	—	1
Saint Mary's	3	—	—	—	4	—	1	—	—	—	2	—	—	1	3	—	—	—	1
Cecil	4	—	—	—	2	2	—	—	—	—	—	—	—	—	1	—	1	—	5
Kent	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	2
Queen Anne's	4	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—
Caroline	2	—	—	—	—	—	—	—	—	—	—	—	—	2	1	—	7	—	1
Talbot	—	—	—	—	—	—	—	—	—	—	—	—	—	1	2	—	5	—	1
Dorchester	1	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	8	—	4
Wicomico	8	—	—	—	1	—	—	—	—	—	1	—	—	—	6	—	10	—	—
Worcester	2	—	—	—	—	—	—	—	—	—	—	—	—	4	—	—	—	—	1
Somerset	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Total Counties	158	0	15	8	309	3	77	1	0	0	40	0	0	12	82	2	49		61
Baltimore City	175	0	28	2	1175	0	161	0	0	0	41	0	0	9	85	17	494		38
State																			
Jan. 1–26, 1956	333	0	43	10	1484	3	238	1	0	0	81	0	0	21	167	19	543		99
Same period 1955	326	0	26	33	67	3	133	1	0	0	372	0	0	44	137	16	590		78
5-year median	395	3	22	29	430	7	155	1		0	172	1	1	52	148	24	540		60
Cumulative totals																			
State																			
Year 1956 to date	333	0	43	10	1484	3	238	1	0	0	81	0	0	21	167	19	543		99
Same period 1955	326	0	26	33	67	3	133	1	0	0	372	0	0	44	137	16	590		78
5-year median	395	3	22	29	430	7	155	1		0	172	1	1	52	148	24	540		60

Blue Cross - Blue Shield

SELLING BLUE SHIELD

R. H. DABNEY*

In past reports published in the MEDICAL JOURNAL, we have confined our discussions largely to the general concepts and objectives of Maryland Blue Shield. Not much has been said about our practical efforts in the field to sell Blue Shield. In fact, "selling" Blue Shield is still a harsh sound to those who are not aware of recent trends.

Blue Shield, like Blue Cross, is sponsored at the source of health care. For Blue Cross, it is the hospitals. For Blue Shield, it is the medical profession with organizational approval through the state and component medical societies and with operational sponsorship through actual participating physician agreements. This direct physician sponsorship embodied in written contracts with Blue Shield offers unique guarantees to the public.

Without such active sponsorship, Blue Shield would not have its special identity and in today's competitive market for the consumer's health dollar, there would be nothing unique for this non-profit health service plan to offer to people in the community.

Blue Shield offers people everywhere in the community an effective way to budget in advance for physicians' services. The focus, of course, is on the subscriber and his needs. What he pays for his Blue Shield membership—his subscritpion rate—and what he finds available in his membership—his benefits—are determined on a local basis, so that in every important sense Blue Shield is a community program offering community benefits at community rates through group and non-group membership.

To date, Blue Shield has placed prime emphasis on in-hospital care, and today's Blue Shield program is a broad program including all the basic elements of professional care—surgical, medical, obstetrical, anesthesia, and consultations—for hospitalized patients.

* Executive Director, Maryland Hospital Service, Inc., Maryland Medical Service, Inc.

Add *service benefits*, the benefit feature which so clearly distinguishes Blue Shield from commercial insurance, and you have the practical basis for "selling" Blue Shield as the companion to non-profit Blue Cross. Enrollment progress to date is largely attributable to physician sponsorship and to plan management, working together to "sell" this program on this basis.

On the whole, membership has grown at a rapid rate, give or take some significant peaks and valleys. But let's look at the record, for the record itself is the best indication we have for an analysis of the role that Maryland Blue Shield should play in the future.

Blue Shield enrolled its first subscriber in Maryland in November 1950. Initially, enrollment progress was slow for two basic reasons. First, we were a little late in getting Blue Shield organized in Maryland, and many of our Blue Cross groups had already rounded out their hospitalization coverage with a commercial program covering surgical care. Secondly, our initial program was largely an experimental one, and we had a real "selling problem" in explaining its unique features to our groups.

In the fall of 1951, just one year after we began operations, we undertook a complete re-evaluation of the fee schedule and other areas of the program, culminating in a revised Blue Shield Plan, which was put into effect September 1, 1952. Up to that date we had enrolled some 70,000 subscribers.

Since September 1952, we have successfully directed our major enrollment efforts towards selling Blue Shield to our existing Blue Cross groups. Our enrollment staff, having gained experience and insight during the first two years of Blue Shield, now set their sights on selling Blue Cross *and* Blue Shield, each on its own merits, but together as a health package. We were helped by the ever-increasing emphasis on health insurance in employee benefit programs, and the trend toward joint employee-management financing of the costs. Blue Shield, offering comprehensive benefits for professional care at low subscription rates and on a non-profit basis like Blue Cross, had the answer. Here was a program that had physician sponsorship

and participation, and provided full coverage to persons of low and moderate income. Its unique service benefits played an important part in convincing management that Blue Shield was the best program for their employees.

Meanwhile Blue Cross enrollment, which had shown tremendous gain in the 1947–1951 period, began to slow down. If we were to sell both of these programs to the community, if we were to re-vitalize Blue Cross and Blue Shield concepts and objectives in the public mind, we felt it urgent to use more intensive approaches in the ever-broadening (and competitive) market. Together with other Blue Cross and Blue Shield Plans, we embarked on a national advertising program in the spring of 1954, using the popular consumer magazines. In the summer of that year, we undertook a local advertising program, using newspaper and radio throughout the State. As an opening gun, we announced a new program for non-group, or individual enrollment.

After the first impact of these educational and promotional campaigns, both Blue Cross and Blue Shield enrollment began to rise. In 1955 alone, Blue Shield membership increased by some 84,000, which was a gain of over 40% from the previous year. Blue Cross membership increased by approximately the same amount, a smaller percentage gain because of the larger size of the Plan, but nevertheless the largest net gain since 1950.

Blue Shield membership now stands at 344,000 in Maryland, or roughly 36% of the Blue Cross membership of 941,000. We have come a long way since September 1952, but we still have our greatest period of growth ahead. With continued physician sponsorship and support, we can look forward to substantial further growth in the year ahead.

ANNUAL MEETING EXHIBITORS

(As of January 1, 1956)

MAY 2, 3, 4, 1956

ABBOTT LABORATORIES
A. S. ALOE COMPANY
AYERST LABORATORIES
BABY DEVELOPMENT CLINIC
THE BAKER LABORATORIES, INC.
BRAYTEN PHARMACEUTICAL COMPANY
A. J. BUCK & SON
CIBA PHARMACEUTICAL PRODUCTS, INC.
HERBERT COX—CORRECT SHOES
DESITIN CHEMICAL COMPANY
DOHO CHEMICAL CORPORATION
EATON LABORATORIES, INC.
C. B. FLEET COMPANY, INC.
GRAYMAR COMPANY
HYNSON, WESTCOTT & DUNNING, INC.
KLOMAN INSTRUMENT COMPANY, INC.
LEDERLE LABORATORIES, DIVISION, AMERICAN CYANAMID COMPANY
THE LIEBEL-FLARSHEIM COMPANY
ELI LILLY AND COMPANY
MEAD JOHNSON & COMPANY
MURRAY-BAUMGARTNER SURGICAL INSTRUMENT COMPANY, INC.
PFIZER LABORATORIES, INC.
WILLIAM P. POYTHRESS & COMPANY, INC.
A. H. ROBINS COMPANY, INC.
J. B. ROERIG AND COMPANY
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Ancillary News

NURSING SECTION

M. RUTH MOUBRAY, R.N., *Executive Secretary,*
Maryland State Nurses Association

ANNUAL CONVENTION OF THE MARYLAND STATE NURSES ASSOCIATION AND THE MARYLAND LEAGUE FOR NURSING*

The Maryland State Nurses Association decided at its annual business meeting not to undertake to secure any changes in the nursing practice act during the session of the General Assembly of Maryland occurring in 1956. A recent interpretation by the State Law Department of the three-year time requirement will permit the Maryland State Board of Examiners of Nurses to decide whether the time requirement for the preparation of registered nurses shall be three calendar years or three academic years.

Speakers for the convention included the following: Dr. Weston LaBarre, Associate Professor of Anthropology, Duke University; topic, "Nursing and Society." Dr. Louis A. M. Krause, Professor of Clinical Medicine, University of Maryland; topic, "Nursing—Its Past, Present and Future." Miss Katharine A. Lembright, Assistant Executive Secretary, Industrial Nurses Section of the American Nurses' Association; topic, "A Place for All." Miss Frances L. George, Professor of Nursing Education, University of Pittsburgh; topic, "Looking Ahead in Nursing Education and Nursing Service."

Miss Bernice E. Anderson, Associate Professor of Nursing Education, Teachers College, Columbia University, topic, "We Can Have More Flexible Educational Standards for Schools of Nursing." Miss Mildred Montag, Director Cooperative Research Project, Junior and Community College Education for Nursing, Teachers College, Columbia University; topic, "Cooperative Research Project, Junior and Community College Education for Nursing."

* November 2–4, 1955 at the Emerson Hotel, Baltimore, Maryland.

Miss Ruth B. Freeman, Associate Professor of Public Health Administration, The Johns Hopkins School of Hygiene and Public Health presented a very challenging Report of a Survey on Interest and Needs for Continuing Education for Nurses in Maryland. A copy of Miss Freeman's report can be obtained from the Maryland League for Nursing, 1215 Cathedral Street, Baltimore 1, Maryland. Miss Freeman is at present the President of the National League for Nursing. It is a real privilege to have her with us in Maryland.

A panel discussion on the topic, "Resources to Meet the Needs of the Emotionally Disturbed School Age Child" was received with much interest. Participants in the discussion were Dr. Robert E. Thomas, Chief, Division of Mental Health, Maryland State Department of Health; Mr. Thomas J. S. Waxter, Director, State Department of Public Welfare; Dr. David Vaile, Clinical Director, Rosewood State Training School; Dr. Arthur Lichtenstein, Director of Special Services, Baltimore Department of Education; and Miss Florence Burnett, Public Health Nursing Consultant in Mental Health, Maryland State Department of Health.

The Student Nurses Council of Maryland had an enthusiastic meeting at which Mr. Dwight P. Jacobus, Supervisor of Educational Services to Industry, Maryland State Department of Education, moderated a discussion on "Interpersonal Relations." The Council also held a talent show at Lutheran Hospital Nurses Residence.

MARYLAND STATE NURSES ASSOCIATION

Officers and Section Chairmen, 1956

President—Miss M. Elizabeth Pickens
First Vice-President—Mrs. Lois W. DeBrule
Second Vice-President—Miss Eleanor J. Smith

Secretary—Miss Ann L. Klingelhofer
Treasurer—Miss Olive M. Smith
Directors—Mrs. Eleanor H. Fox; Sister M. Rosaire Foley; Miss Harriett Hicok; Sister Athanasius Aherne; Miss Katherine Childs; Miss Julia R. Lizer

Chairmen of Sections:

Educational Administrators, Consultants & Teachers—Miss June E. Geiser
General Duty Nurses Temporary Chairman—Mrs. Sarah M. Workman
Industrial Nurses—Miss Margaret E. Kramer
Institutional Nursing Service Administrators—Miss L. Elizabeth Hirst
Private Duty Nurses—Miss Anne H. Cahoon
Public Health Nurses—Miss Catherine D. Crompton

MARYLAND LEAGUE FOR NURSING

Officers, 1956

President—Miss Alice M. Sundberg
Vice-President—Miss Virginia R. Struve
Corresponding Secretary—Miss Pauline V. Kummer
Recording Secretary—Miss Anna C. Scholl
Treasurer—Mr. Robert S. Hoyt

MEDICAL AND CHIRURGICAL FACULTY ANNUAL MEETING DATES

MAY 2, 3, 4, 1956

BUSINESS MEETINGS—Wednesday and Friday mornings, May 2 and 4, 1956
SCIENTIFIC SESSIONS—Wednesday afternoon, May 2; all day Thursday, May 3; and Friday afternoon, May 4, 1956.
WOMAN'S AUXILIARY LUNCHEON—Wednesday, May 2, 1956.
ROUND TABLE LUNCHEON—Thursday, May 3, 1956.
PRESIDENTIAL DINNER and MEETING—Thursday, May 3, 1956.
AUXILIARY BALL—Friday evening, May 4, 1956.

ANNOUNCEMENT

April 2, 1956

One Week Intensive Course in the Diagnostic Use of Radioactive Iodine—I^{131}

By

BENEDICT J. DUFFY, JR., M.D., *Director* JOHN R. HOWLEY, *Physicist*

Isotope Laboratory, Georgetown University Medical Center, Washington 7, D. C.

Subject to the receipt of sufficient registrations, a One Week Intensive Course in the Diagnostic Use of Radioactive Iodine (I^{131}) has been scheduled to begin April 2, 1956. The course will be presented in the Isotope Laboratory at the Georgetown University Medical Center, where a large volume of clinical material is constantly available.

Woman's Auxiliary Medical and Chirurgical Faculty

MRS. ALBERT E. GOLDSTEIN, *Auxiliary Editor*

PUBLIC RELATIONS IN THE AUXILIARY

MRS. JOHN G. BALL*

You are Public Relations! It is your responsibility, your job, your life. Each woman is interested in her home, husband, family and church. After these "firsts" come the community in which she lives and the problems of the community which affect her home and family. A physician's wife has the additional responsibility of taking an active interest in her husband's profession. Public Relations is every Auxiliary member's job. What she does with her spare time, how she meets paitents, answers the door, the telephone, talks with friends, works in citizen groups, church and club groups, promote understanding between the medical profession and the public. A physician's wife is her husband's community envoy and representative. Too often he is too busy to do his share. Authentic self information is the first step, but it is not enough. After we are informed ourselves, we should transfer that knowledge into community action. Leadership in health education and community health service belongs to the physician's wife.

There are projects which serve the medical profession directly, such as promoting and organizing a Speaker's Bureau. A list of qualified interesting speakers on a variety of health or medical subjects would be welcomed by many community club program chairmen.

The week of April 23–29, 1956, is to be Medical Education Week. This is a joint undertaking of the AMA, the Association of American Medical Colleges, the National Fund of Medical Education and the American Medical Education Foundation. The primary function of this week is to call national attention to the progress, contributions as well as financial plight of our nation's medical schools. The public should know that its own good health is the direct result of the unsurpassed quality of American medical education. The role of the Auxiliary will be one of public relations, not of solicitation, during this week. For the first time the lay public will be solicited on behalf of the nation's 81 medical schools, with the "80 Dimes Campaign." The medical family will be expected to lead the way by contributing to the "80 Dimes Campaign." The danger of Federal encroachment on our medical schools looms ever closer. The recent White House Conference on Education voted that Federal aid was essential to public schools. This should spur us on to do our best to keep our medical schools functioning under private ownership.

Mental Health is a new concern of the Auxiliary. In April, Mental Health Week will be celebrated. Magazines and books are needed by our Maryland State Mental Institutions. The week could be celebrated by collecting this needed material.

Community health education may be promoted by Health Days, distribution of health literature at clubs, county fairs and to friends.

Doctor's Day has been celebrated in Maryland for several years. A suggestion has been made that we call this day "Physician's Day" or "Medical Doctor's Day" so that it will honor medical doctors. Chiropractic, veterinary, naturopathic, osteopathic "doctors" have been including themselves in "Doctor's Day."

The Auxiliary may supply school libraries with literature on health, notably subscriptions to "Today's Health." The availability of lists offering speakers, movies, exhibit materials for health programs to community organizations is a welcome community health service.

Organization of Baby Sitter Course, "Gems," as part of national safety program is an Auxiliary sponsored project.

Nurse recruitment through the Future Nurse Clubs in high schools has been and continues to be an outstanding contribution of Maryland to the National Nurse Recruitment Program. The State

* Chairman, Public Relations Committee, Woman's Auxiliary to the Medical and Chirurgical Faculty.

Auxiliary is now considering a method to enlarge the program to include laboratory technicians and other medically allied professions.

The Auxiliary continues to cooperate with other organizations through its individual members as well as in a group. Many of the health drives for cancer, poliomyelitis, heart, cerebral palsy, multiple sclerosis, have volunteer helpers from the Auxiliary. Civil Defense, Red Cross volunteer services, P.T.A. Health Committees are all part of *our* community responsibility.

A community's needs vary in scope and each Auxiliary must decide where it can do the best work. The size and financial condition of the Auxiliary will also limit its projects. However, each member can become better informed from authentic sources for her own public relations job. The Auxiliary with better informed members will then find its special public relations project from the many available.

REPORT OF WOMAN'S AUXILIARY TO THE PRINCE GEORGE'S COUNTY MEDICAL SOCIETY*

MRS. F. E. MUSSER†

The Prince George's County Auxiliary is small but active in Nurse Scholarship and public relations.

The program for 1955–1956 is a varied one. The first meeting is always a luncheon meeting held at the local country club. At this time we have the opportunity to become better acquainted with the state president and renew acquaintances with auxiliary members after the summer recess. Subsequent monthly meetings are held in the homes of auxiliary members which inspires a warm friendly atmosphere.

Currently we are planning and organizing the annual fund raising card party. We anticipate the usual pleasant and profitable afternoon for everyone.

Mrs. Henry Wolfe and her committee are responsible for the refreshments, prizes, baked goods table and white elephant table. Proceeds from this project are used for a nurse scholarship each spring.

There are additional plans for a Christmas Party, a book review, a program on mental health, and in case of an open meeting, we will have a hobby demonstration in ceramics. In May we plan to give a tea in honor of the senior members of the Future Nurses Clubs. At this time we have the opportunity to meet the girls who are interested in a nurse's career. In addition, we will witness the presentation of nurses scholarships given in this county through the Prince George's Auxiliary. This tea is one of the rewarding highlights of the year.

Mrs. Thomas Christensen, Nurse Recruitment Chairman, has organized five Future Nurses Clubs.

On Doctors' Day, March 30, 1956, the doctors' wives will serve the luncheon to their husbands in the hospital conference room. Mrs. John Haught, Doctors' Day Chairman, and her committee will pin a red carnation on each doctor's lapel. This is always a lovely occasion.

The past and the future promise an active, cooperative and rewarding year in Prince George's County.

* This is one of a series of reports from the Component Auxiliaries.

† President, Woman's Auxiliary to the Prince George's County Medical Society.

JOINT EVENING MEETING OF THE BALTIMORE CITY MEDICAL SOCIETY AND THE WOMAN'S AUXILIARY TO THE BALTIMORE CITY MEDICAL SOCIETY

MRS. CONRAD ACTON*

For the spice of variety, the Woman's Auxiliary added a new touch for December, and held its meeting in the evening, in conjunction with the regular meeting of the Baltimore City Medical Society, a husbands-and-wives arrangement that, it was felt, helped to augment the attendance at both meetings.

Dr. Russell S. Fisher, Chief Medical Examiner for the State of Maryland, was the speaker for the women's group, and he gave a fascinating account, illustrated with slides, of "Medicolegal Investigations." Following this, the ladies joined the men in the supper room for refreshments, and a view of the art and flower displays loaned by the members of the Auxiliary.

A special vote of thanks is hereby tendered the Hospitality Committee of the Auxiliary, Mrs. William D. Lynn and Mrs. Raymond V. Rangle, Chairman and Co-Chairman, for the delicious refreshments they provided.

The evening meeting was tried as an experiment, and proved so interesting and successful, in many ways, that it may be tried again.

* President, Woman's Auxiliary to the Baltimore City Medical Society.

COMING MEETINGS

OTOLARYNGOLOGICAL SECTION

WALTER E. LOCH, M.D., *Chairman* THEORDORE A. SCHWARTZ, M.D., *Secretary*

Tuesday, March 6, 1956, 6:00 p.m.

Homewood Campus, Dinner Meeting

Diseases of the Salivary Glands. James H. Maxwell, M.D., Professor of Otolaryngology, University of Michigan School of Medicine

SECTION ON DISEASES OF THE CHEST*

MILTON KRESS, M.D., *Chairman* EDMUND G. BEACHAM, M.D., *Secretary*

Wednesday, March 7, 1956, 8:00 p.m.

Faculty Building, 1211 Cathedral Street, Baltimore

Effect of Pulmonary Irritants. (Illustrated) James P. Isaacs, M.D., Instructor of Surgery, The Johns Hopkins University School of Medicine.

COMMITTEE FOR THE STUDY OF PELVIC CANCER

RICHARD W. TELINDE, M.D., *Chairman* BEVERLEY C. COMPTON, M.D., *Secretary*

Thursday, March 15, 1956, 5:00 to 6:00 p.m.

Faculty Building, 1211 Cathedral Street, Baltimore

Sponsored by the Maryland Division of the American Cancer Society and the Medical and Chirurgical Faculty.

DERMATOLOGICAL SECTION*

MORRIS M. COHEN, M.D., *Chairman* STANLEY N. JAFFE, M.D., *Secretary*

Monday, March 19, 1956, 8:30 p.m.

Faculty Building, 1211 Cathedral Street, Baltimore

Gamma Globulin and Its Relation to Skin Diseases. Milton S. Sacks, M.D.

MATERNAL MORTALITY COMMITTEE

HUNTINGTON WILLIAMS, M.D., *Chairman* GEORGE H. DAVIS, M.D., *Secretary*

Thursday, March 22, 1956, 4:00 p.m.

Faculty Building, 1211 Cathedral Street, Baltimore

Joint Committee on Maternal Mortality of the Baltimore City Medical Society and Baltimore City Health Department

* Section of the Baltimore City Medical Society.

SECTION ON INTERNAL MEDICINE*

EDWARD F. COTTER, M.D., *Chairman* KATHERINE H. BORKOVICH, M.D., *Secretary*

Tuesday, March 27, 1956, 8:15 p.m.

Faculty Building, 1211 Cathedral Street, Baltimore

Some Problems in Fat Absorption (Illustrated). Albert I. Mendeloff, M.D.

Further Studies on the Diagnosis of Hypertension Caused by Unilateral Renal Disease. Thomas B. Connor, M.D., William C. Thomas, Jr., M.D., and John Eager Howard, M.D.

A short business session will follow the scientific program.

CENTENNIAL CELEBRATION

HAWAII MEDICAL ASSOCIATION

April 22 to 29, 1956

Treat yourself to a week or two in Hawaii in the springtime, why don't you?

That's an invitation it's a pleasure to pass along. It comes from the Hawaii Medical Association, whose members are celebrating their organization's Hundredth Anniversary this coming April 22 to 29 in proper "Hawaii" as well as medical fashion. There will be a short but worthwhile professional program on Monday and Tuesday mornings, a spectacular Centennial Celebration Pageant Tuesday night, and a traditional *luau* (Hawaiian feast to you Easterners) Thursday night, with Polynesian entertainment.

This is the best time of the year to visit America's island paradise—clear, balmy days and cool, refreshing nights; spring flowers in profusion on the ground and in the trees; lovely island m - - but you have the idea now, surely. Hawaii in the spring is always the greatest, and this is your chance to tie it into a professional meeting. It follows the American College of Physicians' session in Los Angeles, too. Write the Hawaii Medical Association, 510 South Beretania St., Honolulu 13, Hawaii, for reservations application forms.

POLIO AHEAD: THE REASONS BEHIND THE 1956 MARYLAND MARCH OF DIMES*

Hart E. Van Riper, M.D.

More cases of polio were reported in Maryland in 1955 than in 1954. It may be presumed that Maryland will still have polio problems in 1956. The Salk vaccine has proved to be a major weapon against paralytic poliomyelitis, but it has not yet won the war against this disease.

Continuing cooperation of physicians must be had both in administering the vaccine and in caring for patients already paralyzed and *who will be* paralyzed in spite of the vaccine. The Salk vaccine is not 100% effective and it will take considerable time yet, perhaps years, before all individuals most susceptible to paralytic poliomyelitis can be fully immunized against it.

The National Foundation for Infantile Paralysis, supported through public contributions to its January March of Dimes, has made an enviable record, both in this state and nationwide, for meeting the problems posed by paralytic polio. In 1955 the March of Dimes gave over 232,000 cc. of Salk vaccine without charge to the state of Maryland to initiate a statewide vaccination program. In addition 27,000 cc. of gamma globulin were supplied.

The results already reported from the use of the vaccine are most encouraging but they must not be allowed to blind the eye of the medical profession to the road that still lies ahead. There remains a great need for additional research to improve the Salk vaccine, to determine the duration of immunity it effects (and conversely to determine the need for "booster shots") and to provide the best possible treatment for patients already or yet to be involved with paralytic poliomyelitis. There is also a vast need for the professional education of young men and women who will contribute to the necessary research and help give the needed treatment.

To pay for research, education and aid to polio patients, the March of Dimes needs $47,600,000 in 1956. Maryland physicians, knowing both the need and the record, will want to support and urge their patients to support the 1956 March of Dimes in their own communities.

A brief review of the record of the National Foundation for Infantile Paralysis in Maryland, where it has 24 local chapters, should help to orient physicians to the many services to patients and the professions which have been made possible by the March of Dimes since 1938, when the National Foundation was founded.

About $2,670,000 has been spent by local chapters in Maryland for the care of polio patients.

A total of 85 National Foundation scholarships and fellowships has been awarded to Maryland residents.

A large amount of research has been conducted in Maryland with the help of March of Dimes grants. Johns Hopkins University, for example, has had over $1,960,000 in March of Dimes grants for virus research which is continuing. Significant steps along the road to a safe and effective polio vaccine were made here. The University of Maryland has had March of Dimes grants of more than $276,000 for research in the after-effects of poliomyelitis. Other Maryland institutions that have had March of Dimes grants are the Children's Hospital of Baltimore and the Microbiological Institute.

Emergency aid in dollars and in equipment (such as respirators) for polio patients has been generously supplied to Maryland. In the first 11 months of 1955, for example, a total of $48,975 in emergency aid was sent to 5 Maryland chapters by the national headquarters of the National Foundation. In the year 1954 the amount was over $72,000 to 6 chapters.

A total of 10 tank respirators, 15 chest respirators and 3 rocking beds was sent into Maryland as emergency shipments in the first 11 months of 1955. The previous year Maryland got 35 respirators.

* The National Foundation for Infantile Paralysis, 120 Broadway, New York, N. Y.